

The Journal of Informed Pharmacotherapy

The World's First Peer-Reviewed Online Journal
Dedicated to Pharmacotherapy

CURRENT ISSUE

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**The world's first completely online peer-reviewed journal
dedicated to pharmacotherapy.**

ISSN 1492-2525

[Current Issue 2002;11 \(Oct- Dec\)](#)

Updates to each issue are made continuously, so
check back often.



Please direct any inquiries or comments about the Journal to the Publishing Editors. We would be happy to send you a more complete description of the Journal which should answer many of your questions.

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Search the Journal of Informed Pharmacotherapy

A brief [explanation](#) of the query language is available, along with examples.

Search for:

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Query Language

The text search engine allows queries to be formed from arbitrary Boolean expressions containing the keywords AND, OR, and NOT, and grouped with parentheses. For example:

information retrieval

finds documents containing 'information' or 'retrieval'

information or retrieval

same as above

information and retrieval

finds documents containing both 'information' and 'retrieval'

information not retrieval

finds documents containing 'information' but not 'retrieval'

(information not retrieval) and WAIS

finds documents containing 'WAIS', plus 'information' but not 'retrieval'

web*

finds documents containing words starting with 'web'

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Frequently Asked Questions about the Journal of Informed Pharmacotherapy

What is the JIP?

- The JIP is a peer-reviewed online journal dedicated to the practice of rational pharmacotherapy through the use of evidence-based principles.
- The JIP fosters the rapid widespread dissemination of original research findings, as well as information intended to help pharmacotherapy practitioners (i.e. pharmacists, physicians, nurses and other health care providers) provide better care for their patients.

Why was the JIP created?

- The idea for the Journal arose out of a recognized need for the following:
 - A new peer-reviewed journal that focuses on pharmacotherapy
 - A journal that provides pharmacotherapy literature reviews which highlight, condense, interpret and put this information into proper perspective using evidence-based principles.
 - An alternative to traditional hardcopy distribution to facilitate the **rapid** and **worldwide** dissemination of original research activity reports.
 - A journal that is accessible to all, for a price that all can afford

What is the history of the JIP?

- The idea for the JIP was originated in late 1998 by the Founding Editors (top left of this page). Since then, the Founding Editors have been busy forming an editorial board and the processes by which the JIP will fulfill its mission.

Who is expected to read the JIP?

- The JIP is intended for any health care professional with an interest in optimizing pharmacotherapy.

What makes the JIP unique?

- JIP is the only peer-reviewed online journal devoted entirely to pharmacotherapy
- JIP provides a strong evidence-based perspective through peer-reviewed research and reviews of the pharmacotherapy literature which put the research findings into their

proper context

- JIP provides a venue for clinicians to widely disseminate research findings (the second it is placed on the Web, it is accessible from any internet terminal on the planet).
- JIP provides more rapid dissemination of information than traditional print journals (for example, we expect turnaround time for articles to be a few weeks, vs. a few months for old-style journals)
- JIP does not require a paid subscription to access

Is the JIP linked to the Pharmaceutical Industry?

- No. There is no financial relationship between the JIP and any pharmaceutical company.
- As with other respected peer-reviewed journals, relationships between authors and such companies must be declared in writing at the time of submission and the details will be provided to the readership in conjunction with any resulting publications.

How is the JIP organized?

- The day-to-day operations of the JIP are run by the Founding Editors on a voluntary basis.
- Section Editors have been selected based upon their recognized clinical and research expertise in a specific area of pharmacotherapeutics (e.g.. cardiology, infectious diseases, toxicology, etc.)
- Section Editors are drawn mainly from the United States and Canada.
- Expert reviewers have been drawn from the global pool of pharmacotherapeutics practitioners and researchers.



What are the responsibilities of JIP Section Editors?

- As a Section Editor, commitment to the following is required:
 - A new peer-reviewed journal that focuses on pharmacotherapy
 - Coordinate the assessment of submissions related to your area of specialty. This involves approximately 2-3 submissions per year.
 - Identify and facilitate the involvement of 2-3 reviewers for each submission sent to you.

- Provide your own recommendation as to the suitability of each submission for publication.
 - By invitation or voluntarily provide other input related to your specialty area such as evidence-based reviews of the pharmacotherapeutic literature, reviews of websites or editorials.
 - Provide a review turnaround time of 4 weeks or less to ensure a prompt (but thorough) review of each submission.
 - Be conversant in the use of email (including the ability to send and receive file attachments) and the internet and have ready access to both. All submissions to the Journal must be in Microsoft Word 97/2000 format, so editors/reviewers must have access to and skills in using this word processing software.
 - Be willing to make a one year commitment to participation as a Section Editor.
- Although these responsibilities may sound onerous, there are several Section Editors and most of the administrative duties are handled by the Managing/Founding Editors. Accordingly, the workload for Section Editors should be manageable.
 - Regardless of whether you are called upon to provide input to the Journal, you would be listed as a Section Editor in all issues of the Journal on the website.
 - **More details about reviewer responsibilities.**

What is the format of the JIP?

- Articles will be published on the Web in browser-friendly HTML format and in a downloadable PDF (Adobe Acrobat) document format.

What types of information does the JIP contain?

- **PEER REVIEWED ORIGINAL RESEARCH ARTICLES**
- **EVIDENCE-BASED REVIEWS OF THE PHARMACOTHERAPEUTIC LITERATURE**
Evidence-based reviews of the pharmacotherapeutic literature with emphasis on interpretation of the findings, designed to help practitioners put the findings into proper perspective. Written by experts in the field.
- **ISSUES IN PHARMACOTHERAPY PRACTICE**
Articles from a variety of sources focusing on therapeutic reviews, practice-related issues, an controversies. These articles undergo editorial review prior to publishing.
- **RESEARCH ABSTRACTS**
An opportunity for researchers to rapidly disseminate their findings in abstract form.
- **PHARMACOTHERAPY ON THE WEB**
Reviews of pharmacotherapy-related websites and other online clinical information resources. Designed to aid practitioners in finding high-quality information as well as using for the internet to enhance their practice.
- **E-MAIL TO THE EDITOR**
Allows rapid interpretation, criticism, and discussion of articles in the Journal (or otherwise) by readers.

What about Permanence?

- One of the primary problems with electronic publication is the difficulty guaranteeing permanence. For many, the fear that a journal may disappear after a short period of publication is enough to deter subscription or submission to that journal. This is particularly a problem for independent journals which often do not have the technical infrastructure or expertise to guarantee permanence.
- The JIP will address this issue by using the Journal Backup service provided by the [International Consortium for Alternative Academic Publishing \(ICAAP\)](#) which provides a backup service which ensures the latest version of this publication will always be available at a central location. In addition to ensuring quick access, this also provides the service of ensuring continuity of access even if we discontinue publication.
- The site will also be "mirrored" through the [ICAAP](#) mirroring service. With this service, I.C.A.A.P. provides fast North American mirrors for international users. Mirrors are essentially duplicate copies of the original publications housed on alternate servers. Users choose the server closest to their geographic location thereby increasing speed of access and visibility.

Why should authors consider submitting articles for publication in the JIP?

- If accepted, authors can expect to have their articles available to a worldwide audience within a few weeks of submission
- Authors will have their articles reviewed by established experts in their field
- Authors can expect to be amongst the first to have articles published in a online peer-reviewed journal
- Authors will support the principles of [alternative academic publishing](#), thereby slowing the decay in our university library systems caused by exorbitant subscription fees charged by publication houses for traditional print journals.

How does the JIP peer-review process work?

- Articles submitted for peer review will undergo a rigorous traditional peer review process intended to minimize the likelihood of release of scientifically unfounded or biased results while minimizing the time it takes to make valid results available.
- Generally, the process looks something like this:
 1. Founding editors review submission for worthiness of external peer-review.
 2. If deemed worthy of peer-review, blinded review by at least two experts in the therapeutic area concerned is conducted.
 3. Feedback from reviewers is received by Founding Editors and publication-worthiness is assessed.
 4. If deemed potentially worthy of publication, comments and suggestions from reviewers are collated and conveyed to the author.
 5. If the author wishes to address the comments / concerns raised by the JIP reviewers, he/she edits the document as appropriate and sends it back to the founding editors.
 6. If the reviewer's concerns have been substantially addressed, the article undergoes final editing and is released for publication. If there is still concern that the reviewers comments have not been properly addressed, the article may be sent back to the reviewers for their input.
- **See the [JIP's detailed peer-review algorithm](#) in PDF format.**

How are JIP citations referenced and cited?

- Since issues of the JIP are dynamic in the sense that they are built up over time as the articles are completed, we have devised a system that should still make it easy to identify and cite JIP articles
- Articles published during each calendar quarter (i.e. 3-month period) will be identified by year, issue (1-4) and page numbers according to the Vancouver
- Page numbers will be assigned sequentially from the first article in the issue through to the closing date for that issue
- Thus, JIP articles may be cited in the standard Vancouver Group format (e.g. J Inform Pharmacother 2000;3:45-52) or by using standard web citation formats, such as:

Marra C. Public Access Comput Syst Rev [serial on-line] 2000;3(4):109-15. Available from: Public Access Computer Systems Forum PACS-L via the Internet (<http://www.pubaccess.com>). Accessed 29 Nov 1999.

How often is the JIP issued?

- Unlike traditional print journals, articles in the JIP will be issued on a continuous basis. As soon as an article has completed the appropriate review process, it will be posted to the JIP website.
- Delays related to episodic publishing (e.g. monthly editions) are avoided.

How much does it cost to subscribe to the JIP?

- Nothing. The JIP will be accessible at no cost over the internet.
- Users will only be required to have the necessary hardware/software for access purposes.
- A free password-based "subscriber" access system may be set up in the future to allow us to track the nature of our readership, however, no information about our readers will be released to any other agency.

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- [New England Journal of Medicine](#)
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- [Pharmacotherapy](#)
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Evidence-Based Medicine Resources

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For Reviewers

This section contains links to information and functions required by designated reviewers of the Journal of Informed Pharmacotherapy.

Please select from the list below:

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1. Submission to the Journal

The JIP is a peer-reviewed online journal dedicated to the practice of rational pharmacotherapy through the use of evidence-based principles. The JIP fosters the rapid widespread dissemination of original research findings, as well as information intended to help pharmacotherapy practitioners (i.e. pharmacists, physicians, nurses and other health care providers) provide better care for their patients.

The idea for the Journal arose out of a recognized need for the following:

- a new peer-reviewed journal that focuses on pharmacotherapy;
- a journal that provides pharmacotherapy literature reviews which highlight, condense, interpret and put this information into proper perspective using evidence-based principles;
- a journal that permits clinicians to disseminate non-peer-reviewed research findings rapidly;
- an alternative to traditional hardcopy distribution to facilitate the rapid and widespread dissemination of original research activity reports and;
- a journal that is accessible to all, for a price that all can afford.

All manuscripts must be submitted by email to the Editors, JIP at email address: (*mail to any*

founding editor, click on [Editorial Board](#)). Submissions should be produced using a recognized word processing software (MS Word preferred). Submitted manuscripts will be considered for publication with the understanding that the manuscript have not been published elsewhere (in electronic format or in print) and is not currently under consideration by another journal or publishing company.

Online and Email Submission Forms:

- Pharmacotherapy on the Web
 - [Website Submission Form](#)
- Research Abstracts: Abstract
 - [Website abstract submission Form](#)
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- Evidence-Based Reviews of the Pharmacotherapy Literature
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 - Email Attachment Submission Form (MS Word DOC format)
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2. Publication categories

JIP publishes evidence-based reviews of the peer-reviewed research articles, evidence-based reviews of the pharmacotherapeutic literature, issues in pharmacotherapy, research abstracts, pharmacotherapy on the web, email to the editors. Our aim is to publishing quality communications that improve our understanding and delivery of health care.

3. Criteria for manuscripts

Submitted manuscripts must meet the following criteria:

- a) the material is original;
- b) the writing is clear, concise and unambiguous;
- c) the study methodology is appropriate;
- d) the data are valid;
- e) the conclusions drawn by the authors are reasonable and supportable;
- f) the information is relevant and interesting. All submissions are assessed for publication eligibility using a [standard approach](#).

4. Corresponding author

When electronically submitting a manuscript for publication consideration, designate a corresponding author and provide a complete mailing address, telephone and fax numbers, and an e-mail address for this individual. The corresponding author will be identified as such in the published article and an email address will be identified for this individual. Email addresses

must also be provided for all authors identified on a manuscript.

5. Authorship responsibility, financial disclosure and assignment of one year exclusive license

Each author must read and sign a statement of authorship responsibility, financial disclosure and granting of one-year exclusive license (PDF format). Please print a local copy of this form, complete all pertinent sections and fax all pages to (604) 875-5267.

Unlike most journals, the JIP does not demand that you grant full copyright over your work to the Journal. Instead, we ask that you grant a one-year exclusive license over the material during which time you agree not to publish the material **in any form** anywhere else. The license period begins on the day the manuscript is published in The Journal and ends one calendar year thereafter. After the one year exclusive license expires, you are free to do whatever you wish with the material, including re-publishing it elsewhere in any form and The Journal retains no rights to it. **During the license period, The Journal retains the exclusive right to publish, distribute, promote, and present the material in any way The Journal sees fit to do so.** In the event that the manuscript is rejected by The Journal, The Journal holds no rights to the material of any kind and you are free to publish it however you wish.

6. Editorial Review and Processing

All submitted manuscripts are reviewed according to a **standard procedure**. Manuscripts are initially reviewed by one of the Founding Editors. Manuscripts with insufficient priority for publication will be rejected promptly. The balance of manuscripts are sent by email to a Section Editor who will coordinate a peer review of the manuscript by expert consultants. Manuscript authors and peer reviewer identities are kept confidential. Manuscripts under review are also kept confidential and the details of such are only known to the Editors and the submitting authors. Manuscripts that are subsequently rejected are not returned to contributors. Manuscripts that are accepted may be edited for conform to the Journal style. Authors are provided a galley proof to review in advance of publication and are considered responsible for all statements made in the final publication. As JIP is an online publication only, no reprints are available.

7. Preparing the manuscript for submission

Contributors should prepare their manuscripts in accordance with the **Uniform Requirements for Manuscripts Submitted to Biomedical Journals**. Submit the manuscript as an email attachment file (preferably in MS Word (any version) format). Double-space the text throughout. This includes the title page, abstract, text, acknowledgments, references, tables and figure legends. Use a standard font (e.g. Arial) and a 10- or 12-point font size. On the title page include the full names, highest academic degrees, and affiliations of all authors. If an author affiliation has changed since the work was done, list the new affiliation as well. Use Système International (SI) measurements only, except when dual report is indicated in the SI unit conversion table in these instructions. Use non-proprietary (i.e. generic) drug names, unless the specific trade name of a drug is directly relevant to the discussion. Avoid unnecessary abbreviations. Include a structured abstract of no more than 250 words for reports of original data, reviews and meta-analyses. For other major manuscripts, you may be asked to provide a brief unstructured abstract. Abstracts are not generally required for editorials. For experimental investigations of human or animal subjects, state in the Methods section of the manuscript that an appropriate institutional review board approved the project.

Provide the approval numbers as necessary. For investigations of human subjects, state in the Methods section the manner in which informed consent was obtained.

8. Disclosing funding and support information

Any and all financial and material support for the research and the work should be clearly and completely identified by the corresponding author. In situations where a pharmaceutical company has provided support, details regarding the specific role of the funding organization in the design, conduct, interpretation, and analysis of the study and review or approval of the manuscript must be provided.

9. Referencing format

Number the references in the order that they appear in the text of the manuscript. When listing references, follow the uniform requirements style (the Vancouver style) that is based largely on an ANSI standard style adapted by the NLM for its databases (e.g., MEDLINE).

10. Tables, figures and illustrations

All tables and figures should be numbered in the order of their citation in the text. Include a title for each table and figure.

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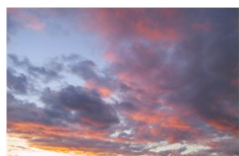
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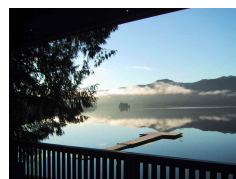
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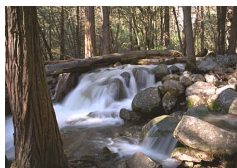


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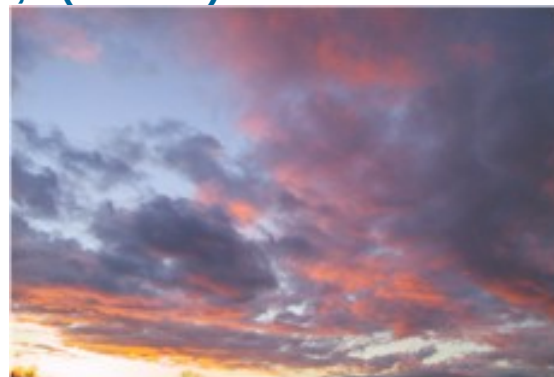
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Editorial

Pharmacist Scope of Practice: A Response to the 2002 ACP-ASIM Position Paper

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Times have changed since pharmacists were primarily concerned with licking, sticking, counting and pouring pharmaceuticals. A shift from a product-centered profession to a patient-centered, outcome-oriented profession is well underway and is already firmly established in institutional practice. In recent years several studies have demonstrated that pharmacists practicing in direct patient care roles as part of multidisciplinary care teams not only reduce overall health care costs but morbidity and mortality as well (1-3). It is perhaps in response to this "pharmacy movement"(4) that in January 2002 the **American College of Physicians-American Society of Internal Medicine (ACP-ASIM) published a position paper** describing their perceptions of the pharmacist's scope of practice (4).

The physician-authored paper accurately presents available data supporting the roles of pharmacists in various patient care settings. It acknowledges the aspirations of pharmacists as described in the American Pharmaceutical Association's definition of pharmaceutical care and upholds the necessity that pharmacists be remunerated for their cognitive services. Wisely, the paper supports that pharmacists take an active role in educating physicians about drug use. Pharmacists as immunization providers is also advocated. The authors even provide a detailed account of the multitude of progressive roles undertaken by pharmacists with the support of state legislatures.

The paper outlines five positions on the scope of pharmacist practice starting with support for research into the effects of pharmacy automation and the move to the all-Pharm.D. degree on pharmacy practice, and concludes with a position reiterating support for therapeutic interchange programs which is similar to the position of the American College of Clinical Pharmacy (ACCP) (5). What lies between these benign stands are more contentious positions concerning collaborative care and the value of pharmacists intervention.

The ACP-ASIM position on collaborative care supports *"physician-directed, pharmacist-physician collaborative practice agreements limited to pharmacists involvement in patient education and hospital rounds under the following conditions: (i) expanded roles of pharmacists should not be solely based on cost-savings; (ii) the responsible physician and pharmacist should be compensated for their time spent on collaborative services; (iii) the physician should solely determine if a relationship will be formed with the pharmacist; (iv) the physician should solely and individually refer a patient to a pharmacist; and (v) only the physician can and will diagnose the patient's condition prior to any referral."*

The idea asserted by the ACP-ASIM that a patient shall not form a relationship with a pharmacist unless authorized to do so by a physician is reduced to absurdity when one considers the following:

1. **The sheer number and accessibility of pharmacists far exceeds that of physicians.** Patients have always sought the advice of pharmacists on a broad range of health issues. In this context, pharmacists have been recommending, initiating, monitoring and modifying drug therapy for decades. They have been independently educating patients about drug therapy all along. Patients have been making informed decisions about prescription and non-prescription drugs based on this information. The pharmacy profession's efforts over the last decade have been aimed at constantly improving pharmacists' skills in providing this type of care. Patients decide whom they wish to consult for health advice and the value of that service to them.
2. **The very act of writing a prescription invokes the formation of a professional relationship between pharmacist and patient and all of the legislated, mandated, ethical and professional responsibilities inherent therein.** Do physicians long for the days past when they could prescribe an NSAID to a patient for joint pain without informing them of the risk of death due to upper gastrointestinal bleeding, expect that the pharmacist won't "undermine" their prescription by doing the same, and assume the patient will faithfully take the drug as directed? The pharmacist's foremost duty is to the patient, not the physician.
3. **In most institutions, the pharmacist's duty to independently assess and strive to ensure appropriate drug therapy on a patient-specific basis is a Medical Advisory Committee decreed policy.** Such policies partially arose from the need to reduce the risk of avoidable adverse drug events resulting from misprescribing by physicians.
4. **Experience dictates that physicians lacking appropriate drug therapy skills are frequently unaware of this deficit.** That these physicians should be relied upon to seek advice and refer patients for pharmacotherapeutic consultation is not in the best interests of patients.
5. **Though we do not assert that all pharmacists are trained as diagnosticians, the reality that pharmacists interpret the complaints of scores of patients every day, form correct diagnoses and initiate and monitor appropriate drug therapy must be acknowledged.** Patients would not tolerate any attempt to limit the pharmacist's ability to provide this advice, nor could any nation's health system bear the cost of having these complaints referred to physicians, as the ASP-ASIM apparently desire.

Pharmacists have already established themselves as direct patient care providers in many settings where justification based on cost savings alone is not necessary (1-3). Despite this, the necessity for provision of cost-effective and safe care in an era of skyrocketing cost and complexity of drug therapy has allowed motivated pharmacists to make great strides in expanding their scope of practice. No data is presented by the authors of the ACP-ASIM paper which assert that the wide variety of initiatives undertaken by pharmacists has resulted in harm or have in any way been detrimental to patients.

Much of the ACP-ASIM's concern centers on the perceived differential between "hands-on" patient care training in PharmD programs and medical schools. The debate about the sufficiency of the pharmacotherapy training imparted in most medical schools is one for another day. The ACP-ASIM's statement that *"physicians are qualified to...treat patients, while pharmacists expertise lies with pharmaceuticals"* is cryptic, and their position that *"decisions about the most appropriate drug therapy for a patient's condition are often subtle and require a level of experience and training that is not*

provided in obtaining a PharmD degree” is objectionable. Neither group has sufficient evidence to properly support or refute ACP/ASIM's antiquated opinions. However, thousands of highly trained, experienced, patient-oriented pharmacists adept at interpreting the subtleties of patients' drug therapy needs are disproving this statement every day.

ACP-ASIM also opposes independent pharmacist prescriptive privileges and initiation of drug therapy. This is not surprising given that this is one of the most sensitive areas of the “turf battle” between the professions, including that brewing between nurses and physicians. As already stated, pharmacists already have prescriptive authority for patients seeking therapy in a community pharmacy in which the pharmacist can prescribe from a wide array of over-the-counter medications. The ACP-ASIM paper nicely catalogues the many other areas where prescriptive authority is being exercised or evaluated, such as emergency contraception, anticoagulation, diabetes management, and numerous other “disease management” programs. The experience being accrued in these and other jurisdictions will ultimately provide the data required to define what initiatives work best, what patients prefer and which result in the best outcomes. The ACP-ASIM's lack of support for these initiatives is out of step with the demand by patients for such services and the reality that patients are already benefiting from them.

ACP-ASIM's statements such as *“pharmacists can educate physicians on drug interactions and cost savings and educate patients on drug safety, while physicians provide safe, effective care to patients”*, fuels exactly the “turf battle” the physicians claim in their paper that they want to avoid. Such marginalizing statements belie the underlying aim of the ACP-ASIM's position, which seems to be to protect the domain of the physician rather than to support a multidisciplinary and balanced approach to patient care. This ridiculous attempt to reduce a profession to discrete tasks such as those named while ascribing to physicians the exclusive right to “provide safe, effective care to patients” shows ACP-ASIM's lack of insight about the rapidly evolving multidisciplinary health system.

What the ACP-ASIM position paper stridently aims to assert is that physicians are already providing high-quality safe, effective drug therapy to their patients and that pharmacists, while potentially helpful (though annoyingly time-consuming (4)) assistants in this regard, ought not to interfere in that provision. The alarming rates of prescription drug-related morbidity and death in North America are a stark reminder that this is not the case (5-14). Informed consumers demand that this situation be improved. Neither physicians nor pharmacists are providing the care necessary to avoid this needless suffering. Turning back the clock on pharmacist roles and limiting access by patients to pharmacists, even if physicians had the authority to do so, would not serve the best interests of our patients.

The ACP-ASIM could be forgiven for their extreme traditionalist positions if they were aimed at the lowest level of pharmacist practice. Indeed, not all pharmacists are sufficiently trained, motivated, experienced, ethical, or skilled enough to provide high-level pharmaceutical care to patients. Neither, for that matter, are all physicians. The profession of pharmacy, like medicine, has evolved to include a wide array of professionals with diverse and varied levels of training, skill and experience. Fortunately, enhanced responsibilities for pharmacists have been limited mainly to those who obtain specialized training and achieve certification in various forms. The position paper; however, purports to describe the “scope of practice” of pharmacists. In this attempt, they have accurately described that scope as it existed 20 years ago. The ACP-ASIM appears to desire a return to a time when pharmacists dutifully told patients in response to their drug therapy questions, “I shouldn't answer that, you'll have to discuss that with your doctor.”

It is doubtful that the conservative and demeaning ACP-ASIM position statement will have much impact on the pharmacy profession who, supported by numerous state and provincial legislatures, have embraced the role of drug therapy providers and competently provide for the needs of their patients. They do this within a complex array of collaborations with physicians ranging from total independence to direct supervision. Ultimately patients, not physicians, will decide which services they value and how much.

Peter J. Zed, B.Sc.(Pharm), Pharm.D.

Peter S. Loewen, B.Sc.(Pharm), Pharm.D.

Publishing Editors

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Reader Responses to the Editorial, "Pharmacist Scope of Practice: A Response to the 2002 ACP-ASIM Position Paper"

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To the Editors:

Congratulations on your recent editorial on the response to the 2002 ACP-ASIM Position Paper on The Pharmacist's Scope of Practice. I very much, as you did, felt that this was a "fearful" response concerning loss of turf and that despite being portrayed as supportive was anything but. It is intriguing to me that the traditional healthcare providers seem to be more concerned about battling among themselves rather than joining forces to deal with some of the nontraditional providers who actually undermine healthcare.

Obviously we have still a long way to go.

Charlie Bayliff
Pharmacist, London Health Sciences Centre
London, Ontario, Canada

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To the Editors:

I think that we need to step back and not be too discouraged by the nature of the ACP paper. I agree with your passionate and eloquent response but we need to remember for every UBC/similarly residency trained +/- PharmD with a few years of practice experience, or keen community pharmacist, there are several pharmacists out there in drugstores and hospitals with limited clinical training bugging physicians multiple times a day with trivial issues or worse, making therapeutic arguments without adequate information or understanding of clinical relevance. There are also an alarming number of pharmacists who, unlike ourselves, do not feel comfortable taking on more patient care responsibility.

They feel sufficiently challenged and busy with the dispensing process and leaving clinical decisions -no matter how minor, to physicians. I think this pattern is limiting the shift of the profession from being product based to knowledge based.

We also have to remember that there are roughly 5,000 more physicians than pharmacists in BC (about 8,000 MSP billers vs. about 3000 pharmacists). So if even half of us take up the call to provide proper pharmaceutical care, we will still be very short-staffed. A case in point was an ongoing discussion I had with a public health physician in charge of a provincial vaccination program a couple of years ago. She was lamenting that they didn't have enough staff to vaccinate all the people that needed vaccination and how poor vaccine record keeping was. I promoted pharmacists to her as great resource to improve things on both fronts. At first she dismissed my suggestion as "not in keeping with the traditional doctor/nurse model". I pointed out the flaw in her logic and she had to agree that pharmacist administered vaccination and record keeping was worth pursuing. Unfortunately, when she did pursue it with the provincial pharmacy organizations, she was told that there was little interest among their members in administering vaccines (citing workload, training and liability concerns). So I felt a bit sheepish to say the least.

Until we get our own house in order - of which the first step is working with the colleges of pharmacists and physicians & surgeons to eliminate regulations that limit the pharmacists ability to make even basic (e.g. dosage form selection) independent pharmacotherapy decisions AND implement regulations recognized by all health professionals that obligate pharmacists to be accountable for clinical interventions - I'm afraid we're at an impasse.

Once pharmacists are gradually held accountable for more & more important clinical decisions, then they will be forced to step up to the plate and embrace pharmaceutical care fully. We won't gain recognition for being able to provide "advanced" patient care until more of us actually do it. Talk is cheap. We're still the number 1 or 2 trusted profession in surveys, so we need to proceed in a manner that maintains that trust in the public's eye - a big part of that is their knowledge that we work co-operatively with their doctors to look out for their best interests.

If you read the editorial in the Feb 19th AIM responding to the ACP position paper by a pharmacist from Walmart in the US; I think that provides a useful first step in this dance with the docs....just having the internal medicine dinosaurs recognize pharmacists is a great opportunity to build on...we have to now win them over one at a time.

Bruce Lange, BSc.Pharm., Pharm.D.

Pharmacotherapeutic Specialist, Royal Columbian Hospital
New Westminster, BC, Canada

To the Editors:

I have recently read your response to the Annals Of Internal Medicine Scope of Pharmacy Practice Paper. To date I have not read a more accurate and truthful analysis of this "paper" and our profession. The two authors are right on the mark with 100% of everything they have written. My only

disappointment is that such a well written and researched response is not more widely available to pharmacists, physicians and patients.

I have taken the liberty to send it to my pharmacy department at Beth Israel Deaconess Medical Center, and it has then been sent to most of the major medical centers in the Boston area. Keep up the good work!

Pharmacy Practice Resident
U.S.A.

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To the Editors:

I have recently read the article published in JIP by Drs Zed and Loewen commenting on the Annals Of Internal Medicine Scope of Pharmacy Practice Paper. What has not surprised me was their passion for advancing the profession of pharmacy, which I absolutely concur with. However, what does concern me is that they had to write this article in the first place.

The profession of pharmacy needs to stand up and re-evaluate what are the priorities. When physician groups are writing position statements with regards to pharmacists roles, we need to take a second look at what we are doing, or at least what physicians think we are doing. When trivial legislation prohibits the pharmacist from making a professional decision, it is not surprising that physicians think most pharmacist "lick, stick and pour".

For example, if a physician writes a prescription for a topical product and it comes as both cream or ointment, the pharmacist is obligated to call and ask the physician "cream or ointment?" ...and probably annoying to the physician. Could not the pharmacist just speak with the patient and together make a decision?

When the patient has no more refills or needs an extension of medication until their next appointment, the pharmacist is obligated to call the physician and probably speaks with the receptionist. Authorization from a receptionist... what's next?

I was recently told of a patient who dropped their tablet of fluconazole on the floor and it got wet. When she called the pharmacist and explained, the pharmacist told her that she needed another prescription in order to give her another tablet. What do you think the physician's perception of that pharmacist is now when she explains to her doctor about what happened?

It is with these attitudes and barriers to the profession that gives other groups the perception that pharmacists are just "paramedicals".

I stand up and applaud Drs Zed and Loewen for showing leadership for pharmacy practitioners who are eager, willing and able to advance our profession. Now every pharmacist and regulatory body should adopt such passionate view points, then maybe we would not be in this situation.

Shallen Letwin, B.Sc.(Pharm), Pharm.D.

Pharmacist

Fraser Health Authority (MSA Hospital)

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To the Editors:

As I read "Pharmacist Scope of Practice: A Response to the 2002 ACP-ASIM Position Paper" by Zed & Loewen, I could not help but again feel ashamed of my profession. How many times are we going to whine about wanting more power? Are we so power hungry that we must get flustered over such an article? Having recently attained my Pharm.D. I can assure you that we are not capable of diagnosing illness. We are not educated in that area. Most schools barely cover enough anatomy to completely understand a disease state. There is a huge amount of detail that is left out for us. There are many variables that pharmacy students are not prepared for. The Pharm.D. students are now being taught how to give an abdominal exam, listen with the stethoscope, and other clinical exams in a one semester course. I would not trust any of them to diagnose my illness. What is the value of that anyway? Do we really think that we are going to catch something that the other 5-6 physicians/residents that check daily are going to miss? Most patients are not comfortable with a pharmacist laying hands on them anyway. Why do we want to bring that dark cloud over this profession anyway?

Diagnosing and prescribing have always been the physician's role. Why suddenly do we wish to take part in those activities? We are specialists in drug regimens and products. We know what is out there, how it works, how much it costs, and the data supporting its efficacy. It is our ability to guide the physician towards appropriate therapy that is our true value. The decision to accept this advice is ultimately up to the physician. A practicing pharmacist can now purchase liability for 2 years for less than couple hundred dollars. Do we as a profession want to be burdened with the incredibly high costs of insurance in order to say we can diagnose and prescribe? In the few states that pharmacists are actually prescribing, how many actually take advantage of it? This profession needs to realize its boundaries and not open up a can of worms in order to fulfill its ego. The doctor must be asked about any changes because he is ultimately responsible. If you really want to play doctor, and are not happy with the defined boundaries of the profession, go to medical school. (physician assistant school might work too)

Leave the rest of us out of it.

Sincerely,

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To the Editors:

There have been several editorials in regard to "Pharmacist Scope of Practice: A Response to the 2002 ACP-ASIM Position Paper" by Zed & Loewen, and many of them thought provoking. However, I write now not to comment on the position paper itself, but on an [editorial by a newly licensed pharmacist from NJ](#). I find it discouraging that a fledgling pharmacist with virtually no practice experience feels he/she so well understands the practice of pharmacy that he/she can so negatively comment on its practice. The commentary clearly demonstrates the individual's limited knowledge of real world practice and reads like a check list of pharmacist responsibilities from a textbook. To think that the interest in collaborative practice protocols is something the profession wishes to "suddenly" partake is but one example of this obvious naiveté.

Like other healthcare professions, the knowledge obtained in formal schooling is but a foundation upon which to build. Post-doctoral training and practice experience are essential in providing quality pharmaceutical care. Pharmacists today are not interested in "playing doctors" as he/she states; those of us extending clinical services have an expertise through which we wish to improve patient care. AT would greatly benefit from participation in a residency program, through which many real world lessons in clinical pharmacy may be learned. Over time, I believe AT will come to appreciate how much one learns through hands-on experience and how much patients do appreciate interactions with pharmacists. It is often the gratitude of patients as well as fellow members of the healthcare team that spurs those of us in the trenches to continue doing what we do.

If AT is ashamed of the pharmacy profession it is due to an obviously disjointed picture created through several academic experiences taken out of context. Hopefully practice experience will bring it into focus.

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Pharmacist Scope of Practice

American College of Physicians–American Society of Internal Medicine*

This paper explores the increased scope of practice of U.S. pharmacists. It presents background information on the pharmacy profession and outlines how the medical profession can work with pharmacists to enhance patient safety and quality of care. The paper calls for further research on the effects of pharmacy automation and the move to the Doctor of Pharmacy degree on pharmacy practice. Other positions include support for patient education and hospital rounds, opposition to independent pharmacist

prescriptive privileges and initiation of drug therapy, increased use of the pharmacist as immunizer (as allowed by state law), and continued support for the American College of Physicians–American Society of Internal Medicine 1990 therapeutic substitution position.

Ann Intern Med. 2002;136:79-85.

Pharmacists, as well as other nonphysician health care providers in the United States, are advocating for increased scope of practice. Their efforts have been successful in several cases. As of early 1999, 24 U.S. states allowed some type of collaborative practice agreement in which physicians delegate patient management responsibilities to pharmacists. The responsibilities range from refill approvals to modification or initiation of patient medication regimens (1) (Appendix).

In addition to broad collaborative agreements, pharmacists are focusing on many other individual practice issues, including prescriptive privileges, disease management, immunization, collaborative drug therapy, laboratory testing and analysis, and patient education. These issues continue to appear in our state legislatures. More than 30 states are expected to consider bills this year to grant prescriptive or independent practice rights to nonphysicians, including pharmacists (1).

THE PHARMACY PROFESSION

Pharmacists practice in various settings, including community pharmacies, hospitals, long-term care facilities, the pharmaceutical industry, mail service, managed care, and government (2). State law regulates the practice of pharmacy, including licensure. To practice pharmacy in any state, a pharmacist must become a registered pharmacist (RPh), also known as a licensed pharmacist. Although requirements vary by state, a licensed pharmacist must, generally, have graduated from

an accredited college of pharmacy, participated in a residency or internship program, and passed the National Association of Boards of Pharmacy Licensing Examination (NABPLEX) (3). In addition, most states require completion of continuing education courses to maintain licensure (3).

All registered pharmacists must hold at least a Bachelor of Science degree in pharmacy, but in 1992, a majority of the nation's pharmacy schools voted to change the only professional degree in pharmacy to the Doctor of Pharmacy (PharmD) degree (4). Programs that confer the PharmD degree require 4 years of education beyond the minimum 2 years of prepharmacy study. Professional courses required for this degree include pharmacognosy, pharmacology, pharmaceutical chemistry, pharmaceuticals, clinical pharmacy, drug information, and pharmacy administration.

In 1976, the American Pharmaceutical Association established the Board of Pharmaceutical Specialties to recognize specialty areas of pharmacy practice. Board certification is a voluntary process for currently licensed pharmacists. The four basic requirements for board certification are an entry-level pharmacy degree, an active pharmacy license, defined additional training and experience in a specialty, and passing the specialty qualifying examination. The Board of Pharmaceutical Specialties currently recognizes five specialty areas (5): 1) nuclear pharmacy (recognized since 1978)—specialists seek to improve and promote the public's health through the

*This paper, written by Johanna L. Keely, MSS, MLSP, was developed for the American College of Physicians–American Society of Internal Medicine Health and Public Policy Committee. Members of the Health and Public Policy Committee were Mary T. Herald, MD (*Chair*); Jeffrey P. Harris, MD (*Vice Chair*); James L. Bernene, MD; David Blumenthal, MD; Charles K. Francis, MD; Carlos R. Hamilton, MD; Martin E. Hickey, MD; Gregory A. Hood, MD; Wayne J. Riley, MD; Philip T. Rodilosso, MD; John A. Seibel, MD; Lee A. Toman, MD; Laurence D. Wellikson, MD; and Winthrop F. Whitcomb, MD. Ex officio members were David J. Gullen, MD (*Chair, Board of Regents*); and Sandra Adamson Fryhofer, MD (*President*). Approved by the Board of Regents on 27 October 2000.

safe and effective use of radioactive drugs for diagnosis and therapy; 2) nutrition support pharmacy (recognized since 1988)—specialists promote the maintenance or restoration of optimal nutritional status, designing and modifying treatment according to the needs of the patient; 3) oncology pharmacy (recognized since 1996)—specialists address the pharmaceutical care of patients with cancer; 4) pharmacotherapy (recognized since 1988)—specialists are responsible for ensuring the safe, appropriate, and economic use of drugs in patient care and frequently serve as a primary source of drug information for other health care professionals; and 5) psychiatric pharmacy (recognized since 1992)—specialists address the pharmaceutical care of patients with psychiatric disorders.

Position 1

The American College of Physicians–American Society of Internal Medicine (ACP–ASIM) supports research into the effects of pharmacy automation and the move to the PharmD degree on pharmacy practice.

Two thirds of pharmacists work in community pharmacies (6). However, it is likely that pharmacists will further branch out into areas such as research, consulting, and hospital work because automation in pharmacy is growing, pharmacy technician responsibilities are increasing, and the PharmD will be the sole pharmacy degree offered in the 21st century.

Pharmacists will be seeking new roles, especially because store-based pharmacists in July through August 1999 spent more than 60% of their time processing and dispensing orders, according to a 1999 survey (7). Clearly, much of this time will be freed up as automated dispensing and use of pharmacy technicians increase. Long-term research is needed to evaluate the effects of automated dispensing and the move to the PharmD on the pharmacy profession. These events will affect not only pharmacy practice but physician practice as well.

PHARMACEUTICAL CARE

Pharmacists are moving from prescription provider to pharmaceutical care provider. The American Pharmaceutical Association defines pharmaceutical care as patient-centered, outcomes-oriented, pharmacy practice. Pharmaceutical care is designed to promote health; prevent disease; and assess, monitor, initiate, and modify

medication use to assure that drug therapy regimens are safe and effective (8). As part of the pharmaceutical care plan, pharmacists help assess therapeutic needs, prevent adverse drug reactions, develop patient-specific therapy, manage chronic disease, and monitor follow-up care (8).

COLLABORATIVE CARE AND THE VALUE OF PHARMACIST INVOLVEMENT

Collaborative drug therapy is one of the best examples of how pharmacists work with physicians. It is designed to maximize the patient's health-related quality of life, reduce the frequency of avoidable drug-related problems, and improve the societal benefits of pharmaceuticals (9). This process involves the pharmacist, physician, other health care professionals, and the patient. It includes basic dispensing functions, drug information services, the solving of patient-related and medication-related problems, and decision making regarding drug prescribing and monitoring and drug regimen adjustments. However, to participate in collaborative drug therapy, pharmacists need access to patients, access to medical records, knowledge and skills, and documentation and compensation for their activities (9).

Collaborative drug therapy covers a wide array of pharmacist activities and takes place in various settings. Several studies have assessed pharmacist participation in drug therapy in different settings, including pharmacy-based disease management and pharmacists on hospital rounds. Generally, pharmacist involvement in drug therapy has been successful, leading to improved patient care and safety and lowered medical costs.

Numerous studies have evaluated the value of the pharmacist in patient care, and they overwhelmingly describe successful ventures, although predominantly in hospital settings. Four clinical pharmacy services were associated with lower mortality rates in hospitals: clinical research, drug information services, medication admission histories, and participation on a cardiopulmonary resuscitation team (10). In addition, six clinical pharmacy services were associated with significantly lower total health care costs: drug use evaluation, drug information services, adverse drug report monitoring, drug protocol management, medical rounds participation, and medication admissions histories (10).

Pharmacist-initiated interventions at a large university hospital significantly decreased drug costs. A study

group randomly assigned to receive pharmacist intervention had 41% lower drug costs than those of the control group. Anti-infective agents had the greatest cost savings (11). The interventions had no effect on length of hospital stay, in-hospital mortality, 30-day readmissions, or the need to readminister the targeted medication or to restart intravenous therapy, but the interventions did provide an equivalent level of care (11). Although the results of this study and others were positive, it is not clear whether pharmacist participation is more effective than more modern interventions that have been shown to improve drug use—namely, computer-generated reminders to physicians at the point of care.

Similarly, pharmacist participation on physician rounds in the intensive care unit has been found useful in preventing medication errors (12). Pharmacists reviewed medication orders at the time of prescribing and made suggestions as necessary. The rate of preventable adverse drug events was reduced by 66%, and physicians accepted 362 of the 365 pharmacist recommendations (12).

In addition to studies of clinical pharmacy services offered in the hospital setting, researchers have also analyzed the effects of pharmacist participation in local clinics and pharmacies, primarily in disease management and immunization. Disease state management credentialing is available for pharmacists through the National Association of Boards of Pharmacy and the National Institute for Standards in Pharmacist Credentialing. Pharmacists may take one of four examinations that are designed to measure knowledge and judgment in providing disease state management services. Examinations are available for anticoagulation, asthma, diabetes mellitus, and dyslipidemia (13).

Pharmacists have been involved in demonstration projects on lipid disorders, anticoagulation clinics, diabetes, asthma, and vaccination (10). These studies indicate that patient outcomes improved and medical costs decreased as a result of pharmacist involvement. By including clinical pharmacists on a heart failure management team, one cardiology clinic significantly reduced all-cause mortality and heart failure events (14).

In addition to heart failure management programs, pharmacists have also been involved in diabetes-monitoring programs. In one study, pharmacists developed a community pharmacy-based diabetes monitoring program. Data on diabetes care were gathered at prescription refills. The average morning blood glucose values

decreased, and a medication adherence rate of 90% was maintained over a 1-year period (15). In addition, pharmacists recommended drug therapies to physicians, and physicians accepted 75% of these recommendations (15).

Position 2

To improve patient safety and reduce medical errors, ACP-ASIM supports physician-directed pharmacist-physician collaborative practice agreements limited to pharmacist involvement in patient education and hospital rounds.

1. *Expanded roles for pharmacists should not be solely based on cost savings.*

2. *The responsible physician and pharmacist should be compensated for their time spent on collaborative services.*

3. *The physician should solely determine if a relationship will be formed with a pharmacist.*

4. *The physician should solely and individually refer a patient to a pharmacist.*

5. *Only the physician shall and must diagnose the patient's condition prior to any referral (16).*

Physicians are qualified to diagnose and treat patients, while pharmacist expertise lies with pharmaceuticals. An improved, more collaborative relationship between the two disciplines could improve patient care and safety and reduce medical costs. However, it is imperative that reduced cost is not the only factor considered in pharmacist scope of practice. In addition, we need to ensure that physicians control prescriptive rights and have the final approval over all patient care decisions. Decisions about the most appropriate drug for a patient's condition are often subtle and require a level of experience and training that is not provided in obtaining a PharmD degree. This, in fact, is why physician training entails many years of practical supervised experience. This is not to say that PharmD training does not add benefit in a collaborative relationship, but rather that the benefit is incremental and not a substitute for that of the physician, whose role is primary.

Pharmacist involvement in patient care activities may improve patient outcomes, but it will also consume physicians' time. For physicians working in a hospital setting, medication advice can be obtained with relatively few diversions from other responsibilities because an in-hospital physician's involvement with pharmacists is largely restricted to the physician's limited time on service and the number of patients on rounds. However,

for physicians in community-based practices, working with pharmacists may present more serious time-management problems. Physicians will have to make decisions based on how much time, realistically, their offices are able to spend working with pharmacists.

Physicians are compensated for time spent working with physician extenders, for example, nurse practitioners and physician assistants. A similar payment system should be established for physicians' collaborative work with pharmacists. Funds should not simply be shifted from one provider to the other; instead, new sources of revenue will need to be identified.

Pharmacists continue to successfully expand their scope of practice. With the transition to the PharmD degree and automated drug dispensing, pharmacists are being trained to take on a greater patient care role. Instead of taking an adversarial position, the medical community must work together with the pharmacy profession to enhance patient care and safety while maintaining physician responsibility for continuous patient care. By combining the efforts of organized medicine and pharmacy, medication errors can be reduced and patients may live fuller, healthier lives.

Simultaneously, the pharmacy and medical professions should use their collective influence to promulgate better education of physicians in the use of drugs. Doing so will reduce medication errors and result in better patient care. Examples of efforts that might occur in this area are working with the U.S. Pharmacopeia and the Food and Drug Administration to promote better reporting mechanisms for drug errors or supporting Centers for Education and Research in Therapeutics.

Position 3

ACP-ASIM opposes independent pharmacist prescriptive privileges and initiation of drug therapy.

Although several studies describe the benefits of pharmacist and physician collaboration, little evidence supports pharmacist prescribing or initiation of drug therapy (10). Physicians have complete medical histories of patients, including awareness of other conditions and past treatments. Without that information, the appropriate training, and the reassurance of patient safety, ACP-ASIM cannot support independent prescriptive authority or drug therapy initiation for pharmacists.

Physician training is rigorous and heavily relies on patient interaction. It entails numerous years of practi-

cal, supervised "hands-on" training because of the subtleties of diagnosis and therapeutics that are the reality of patient care. The insight that this experience provides cannot be replicated in a less time-intensive and rigorous experience. This is not to criticize pharmacist education but instead to emphasize that the goals of the two educational paths are different, as are the outcomes in terms of skill set. Pharmacists do not have the exposure and experience to diagnose and prescribe medications for patients. This is clearly an area that should remain under physician authority.

Position 4

ACP-ASIM supports the use of the pharmacist as immunization information source, host of immunization sites, and immunizer, as appropriate and allowed by state law. ACP-ASIM will work with pharmacy organizations to increase immunization awareness.

Thirty states already allow pharmacists to administer immunizations (17). Because of the extensive state legislation that already exists, allowing pharmacists and nurses to administer immunizations, the potential benefit of nonphysician immunization of patients is widely recognized. Pharmacists provide increased access to immunization through extended business hours and locations. Increased access to immunization by trained pharmacy professionals will help to decrease antibiotic resistance and increase adult immunization. Pharmacists and physicians should focus on delivering vaccines to those populations most at risk, in an attempt to decrease mortality rates from preventable diseases.

Position 5

ACP-ASIM reiterates its support of its 1990 therapeutic substitution position. ACP-ASIM resolves to work with pharmacists in designing therapeutic substitution policies that ensure the highest level of patient care and safety.

Another important issue in physician-pharmacist collaboration is therapeutic substitution—the selection of a chemically different drug that is considered to be a therapeutic alternative with a comparable therapeutic effect. The current ACP-ASIM policy of therapeutic substitution states the following (18):

Position 1. Therapeutic substitution is appropriate only in hospitals with an effectively functioning formulary system and Pharmacy and Therapeutics Committee.

Position 2. Therapeutic substitution jeopardizes patient management when immediate prior consent is not obtained from the authorized prescriber and when documentation of substitutions is untimely or improper. Such practices must not be permitted.

Position 3. The practice of therapeutic substitution may be acceptable in ambulatory settings that meet standards comparable to those of institutional settings.

Position 4. Effective therapeutics require physicians to be well educated in therapeutics and to instruct patients about the proper use and effects of prescribed medication.

The American College of Clinical Pharmacy also supports therapeutic substitution when physicians and pharmacists work together to develop effective policies that maximize patient care at the best price. The American College of Clinical Pharmacy's therapeutic interchange guidelines are as follows (19):

Guideline 1. Therapeutic interchange is appropriate in institutional and ambulatory settings that have a functioning formulary system and Pharmacy and Therapeutics Committee or equivalent advisory committee.

Guideline 2. A continuous drug use evaluation process must be in place for regular review of endorsed therapeutic interchange policies and procedures.

Guideline 3. Therapeutic interchange, as defined herein, may be executed by pharmacists if the authorized prescriber is notified either verbally or in writing within a reasonable time frame, and if the pharmacists have access to medical records and appropriate laboratory or other test results as required by the therapeutic interchange policy. Exceptions to this procedure must be stated clearly in the policy.

Guideline 4. The Pharmacy and Therapeutics Committee or its equivalent should ensure that professional staff are educated regarding the rationale, policies, and procedures for therapeutic interchange.

Guideline 5. The therapeutic interchange policies should define a mechanism that enables authorized prescribers to disallow therapeutic interchange.

Ensuring safe, effective therapeutic substitution is a high priority for both pharmacists and physicians. Immediate prior consent by a physician is essential in maintaining patient management responsibilities and ensuring patient safety. The physician, as patient care manager, and pharmacist, as medication expert, are in a

unique position to work together for improved therapeutic substitution policies that provide high-quality care and cost savings.

REIMBURSEMENT AND LIABILITY

Reimbursement for pharmacists' professional services, other than dispensing, is currently receiving attention by the states. Several states have requested a waiver 11 from Medicaid to develop demonstration projects with pharmacists (20). Mississippi received the first Medicaid waiver (effective April 1998) from the Centers for Medicare and Medicaid Services to reimburse pharmacists for disease management of patients. Reimbursement is available for asthma, diabetes, hyperlipidemia, and anticoagulation services (21). The Mississippi project was an effort to evaluate whether pharmacists are better suited than physicians to cost-effectively spend time educating and monitoring patients.

New Mexico also has a demonstration project that allows pharmacists prescriptive authority according to protocol; however, unlike in Mississippi, pharmacists are not restricted to managing specific diseases (20). Only board-certified pharmacists are allowed to participate, and they must be supervised by a physician approved by the New Mexico Board of Medical Examiners. Pharmacists and physicians meet every 2 weeks, and reimbursement is arranged by physicians.

However, as pharmacists begin to receive reimbursement for their patient care services, they also become increasingly liable for their actions. In January 2000, the Alabama Supreme Court held that pharmacies and pharmacists are "health care providers," thereby governed by the Alabama Medical Liability Act. In August 2000, the Texas Court of Appeals ruled that pharmacists do not have a general duty to warn about all possible side effects or adverse effects but acknowledged that they do have a duty to warn when they are aware of information that would raise the importance or probability of such effects (22). Because reimbursement was not related to the Court's decision, however, payment and liability issues were separated.

Currently, pharmacists are not approved providers under Medicare except to perform immunizations (20). For pharmacists to be added to the list of providers, the Social Security Act would need to be amended. The Centers for Medicare and Medicaid Services implemented a regulation that provides Medicare coverage for

training programs to help beneficiaries with diabetes mellitus to control their disease. Medicare pays certified diabetes educators and dietitians to provide training to help control the disease and avoid complications, such as blindness, amputation, or kidney disease. To be certified, trainers must be employees of a program certified by the Centers for Medicare and Medicaid Services and part of a collaborative team providing services to beneficiaries. Some pharmacists qualify as certified providers if they are a Medicare supplier of durable medical equipment and if they meet quality standards (23).

The Medicare proposal would help newly diagnosed diabetic patients, those who have not received training, or those in serious danger of complications from diabetes mellitus. A physician must certify that a patient needs the service under a comprehensive plan of care. With the approval of their physician or qualified practitioner, eligible beneficiaries would initially receive up to 10 hours of group training and an annual 1-hour refresher course (23).

CONCLUSION

Clearly, pharmacist scope of practice is expanding, and the medical community must proactively respond to the pharmacy movement. The ACP-ASIM remains committed to exploring new roles for nonphysicians and helping to ensure that the practice of medicine remains with physicians. By partnering collaboratively with pharmacists, physicians will be able to avoid “turf” battles and focus on their primary mission—high-quality patient care. Pharmacists can educate physicians on drug interactions and cost savings and educate patients on drug safety, while physicians provide safe, effective care to patients.

However, there are striking differences in physician work settings—that is, hospital versus private practice. Policies must be adapted to meet individual office needs. The ACP-ASIM is committed to fostering effective and productive collaborative relationships between physicians and pharmacists, while securing the physicians’ role as the medical expert who is responsible for the diagnosis and treatment of patients. There is no substitute for medical school training. The ACP-ASIM looks forward to further research on the effect on the pharmacy profession by drug dispensing automation and the move to the PharmD degree. In addition, research evaluating the effects of pharmacist and physician collabora-

tion on physicians’ time with patients and studies examining the outcomes of a community-based PharmD system is needed.

APPENDIX: SUMMARY OF RECENT STATE LEGISLATION Collaborative Practice Agreements

Data in this appendix were obtained from reference 24.

A survey by the National Association Boards of Pharmacy showed that Idaho, Louisiana, Nebraska, Ohio, and Tennessee joined a growing number of jurisdictions permitting pharmacists to develop collaborative practice agreements with prescribers. Such agreements generally allow pharmacists to initiate or modify patient medication regimens pursuant to approved protocol. States also explored this issue in 1999, when 11 states enacted legislation allowing collaborative practice agreements with other health care providers (Arkansas, California, Georgia, Minnesota, Nevada, North Carolina, Oregon, Texas, Utah, Virginia, and Wyoming).

A Minnesota law expanded pharmacists’s scope of practice to include drug administration for first dosages and emergencies and participation in drug-therapy monitoring, selecting therapeutic devices, and drug or drug-related research. This law also permits participation in managing and modifying drug therapy on a case-by-case basis according to a written protocol between the specific pharmacist and an individual practitioner who has prescribing authority and who is responsible for the patient’s care. Virginia authorized pharmacists to enter into collaborative agreements with physicians, osteopathic physicians, or podiatrists. Another law defined “collaborative agreement” and held that such an agreement is not required for the management of patients in an in-patient facility.

Scope of Practice

2000 was an active year for legislation regarding pharmacist scope of practice. Vermont enacted legislation making licensure changes. Arizona enacted a bill changing licensure, fees, and prescription labeling. Georgia now provides qualifications for pharmacists authorized to modify drug therapy. Maryland required pharmacists to maintain a log of new and refill prescriptions. Kansas allowed pharmacists to administer vaccinations to persons 18 years of age or older. Legislation in six states (Alabama, California, Colorado, Delaware, New Hampshire, and Virginia) has passed in at least one chamber. New Hampshire’s bill would allow pharmacists to sell syringes without a prescription, and Virginia’s bill addresses radiopharmaceuticals, prescribers, and distribution.

In 1999, bills relating to scope of practice became law in 17 states (Arkansas, California, Georgia, Louisiana, Maine, Maryland, Minnesota, Missouri, Nebraska, North Dakota, Nevada, Oregon, Tennessee, Texas, Utah, Virginia, and Wyoming).

Areas of expansion of the pharmacist scope of practice included authorization to administer medications and injections, perform physical assessments, and order laboratory tests. Arkansas, California, Georgia, Minnesota, Oregon, Texas, and Utah enacted some provision allowing pharmacists to perform what otherwise have been “hands-on” practitioner activities. Wyoming authorized disease management by adding collaborative pharmaceutical care to the definition of practicing pharmacy. Arkansas codified disease management in its state pharmacy act.

Legislation enacted in Virginia created provisions focusing on the duty of a pharmacist in charge of an automated drug-dispensing system for a hospital. A law in Utah expanded the definition for the practice of pharmacy to include administering and distributing prescription drugs and devices pursuant to appropriate protocols. A law in North Dakota allowed registered pharmacy technicians to receive orally transmitted new or refill prescriptions. A law in Georgia amended several provisions related to pharmacists, including the scope of practice and licensure requirements for nuclear pharmacists.

Maine amended many provisions related to pharmacists and established a statutory review committee to review the scope of practice for pharmacists and, if necessary, to make recommendations for change. The review must address the issues of drug administration and collaborative practice and the current regulatory relationship between the Board of Pharmacy and institutional pharmacies. Effective 6 January 1999, the Alabama Board of Pharmacy adopted regulations that allow pharmacists to provide pharmaceutical care to patients by administering immunizations to eligible patients with valid prescription orders.

Acknowledgments: The author thanks the American College of Physicians—American Society of Internal Medicine Council of Medical Societies—especially D. Craig Brater, MD (*Chair*)—for its contributions to the position paper.

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Original Research Article

Stability of Domperidone in Extemporaneously Compounded Suspensions

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Abstract

Introduction: The recent withdrawal from the market of cisapride has prompted many practitioners to prescribe domperidone as the agent of first choice for patients requiring a gastrointestinal motility-enhancing agent. While domperidone is available in a solid dosage form (i.e. tablet) for oral use, pediatric and other patients who are unable to swallow tablets require an alternative dosage form.

Objectives: To evaluate the stability of 1 and 10 mg/mL domperidone suspensions in a vehicle consisting of equal parts of Ora-Sweet[®] and Ora-Plus[®] after storage at 25°C and 4°C for a maximum of 91 days.

Methods: Suspensions of domperidone 1 and 10 mg/mL, prepared from domperidone maleate tablets, were placed in 50 mL amber plastic bottles. Three bottles of each suspension were stored at 25°C (room temperature) and 3 were stored at 4°C (refrigerated). Physical characteristics including pH, color, odor, viscosity, precipitation, and ease of resuspension were observed weekly for 91 days. Aliquots were removed from each bottle weekly and stored at -85°C until analysis using a high performance liquid chromatography method. A suspension was considered stable if it maintained 90% of its initial concentration.

Results: No change in pH was observed in suspensions of either concentration after storage at 25°C or 4°C for 91 days. Changes in color and odor were not noticeable and viscosity was constant. Precipitates were easily resuspended and there was no caking or clumping of material. Suspensions of both concentrations of domperidone maintained at least 90% of initial concentration at both temperatures throughout the 91-day period.

Conclusions: Domperidone suspensions of both 1 and 10 mg/mL in a 1:1 mixture of Ora-Sweet[®] and Ora-Plus[®] were physically and chemically stable for a period of up to 91 days, both at room temperature and under refrigeration. The expiration date for these products can thus be set at 91 days.

J Inform Pharmacother 2002;8:100-104.

Introduction

The recent withdrawal from the market of cisapride has prompted many practitioners to prescribe domperidone as the agent of first choice for patients requiring a motility-enhancing agent. While domperidone is available in tablet form for oral use, pediatric and other patients who are unable to swallow tablets require an alternative dosage form. As a result of its relative insolubility in water, the alternative oral preparation of domperidone is a suspension. At our hospital, domperidone suspension has been extemporaneously compounded by crushing domperidone maleate tablets and suspending with a methylcellulose vehicle prepared by our pharmacy staff. The suspension was given an empirically-based expiration date of 8 days for refrigerated storage. This short expiration date meant that hospital pharmacy staff had to prepare the suspension frequently and discharged patients had to refill their prescriptions frequently. This, and the additional work in preparing the methylcellulose vehicle, led to relatively high expenditures of both time and money for both parties.

A commercially-available vehicle (1:1 mixture of Ora-Sweet[®]:Ora-Plus[®], a sweetening and suspending agent, respectively) has recently emerged as an alternative to methylcellulose. This newer vehicle eliminates many of the disadvantages associated with methylcellulose, since it is less labor-intensive, is available to both hospital and community pharmacies, and is consequently more convenient for outpatients. However, stability information for domperidone in Ora-Sweet[®]: Ora-Plus[®] does not currently exist.

This study involved an examination of the physical characteristics and chemical stability (defined as maintenance of more than 90% of initial concentration) of extemporaneously prepared oral domperidone suspensions of 1 and 10 mg/mL in a 1:1 mixture of Ora-Sweet[®] and Ora-Plus[®], stored at either 25°C or 4°C throughout a 91-day study period.

Methods

Preparation and Evaluation of Suspension

Domperidone suspensions (1 and 10 mg/mL) were prepared in triplicate from commercially-available tablets of domperidone maleate (Motilium[®], Novopharm, Scarborough, Ontario), containing domperidone 10 mg per tablet, and mixed with equal parts of Ora-Sweet[®] and Ora-Plus[®] (Paddock Laboratories Inc., Minneapolis, MN, lots OE6324 and OH6525, respectively). Six replicates of each concentration were prepared in separate 50-mL amber plastic prescription bottles, three of which were stored at 25°C (room temperature) and three at 4°C (refrigerated). All bottles were exposed only to the fluorescent lights in the laboratory.

Qualitative evaluation of physical appearance took place initially and at weekly intervals up to 91 days. All suspensions were visually examined (against white and black background), for color changes and precipitates, odor changes, layering, sedimentation, ease of resuspension, and gas formation. A fresh sample of each concentration was prepared and compared to a 1 mg/mL sample at 25°C, 1 mg/mL at 4°C, 10 mg/mL at 25°C and 10 mg/mL at 4°C for each of the original samples. Immediately following these physical observations, each suspension bottle was manually shaken for 10 seconds, pH was determined, and

initial and weekly samples were removed and stored at -85°C until batch-analysis by a stability-indicating high performance liquid chromatography (HPLC) method.

Preparation of Stock and Standards

Stock solutions of domperidone at 0.50, 0.250, 0.125, 0.0625, and 0.0312 mg/mL were prepared by dilution of analytical-grade domperidone (Apotex Inc, Toronto, Ontario, lot X99207) in HPLC-grade methanol (Fisher Scientific, Richmond, British Columbia, lot 002129). The internal standard was propranolol (Sigma Aldrich, Oakville, Ontario, lot 90K0523) 0.250 mg/mL in HPLC-grade methanol. Standard solutions were prepared by further diluting a 0.1 mL aliquot of each stock solution and a 0.1 mL aliquot of propranolol 0.250 mg/mL to 1 mL with HPLC-grade methanol to obtain final concentrations of 0.05, 0.025, 0.0125, 0.0062, and 0.0031 mg/mL domperidone. This dilution step was necessary to achieve optimal chromatographics. Prior to injection, all standard solutions were passed through a 0.45-mm microfilter (Acrodisc GHP syringe filter, Gelman, Ann Arbor, Michigan, lot 5874) to prevent injection of impurities onto the column.

The HPLC instrumentation (model 2690, Waters Alliance System, Waters Ltd., Mississauga, Ontario) consisted of a delivery pump, an automatic injector equipped with a 200- μL injector, Nova Pak 3.9 x 20 mm guard column (Waters Ltd., lot W10721), a Nova-Pak C18 3.9 x 150 mm column (Waters Ltd., lot W02901M082), and an ultraviolet detector set at 205 nm (model 2487 dual-wavelength absorbance detector). The mobile phase was developed in the authors' laboratory and consisted of a 45:5:50 (v/v) mixture of methanol (Fisher Scientific, lot 002129): acetonitrile (Fisher Scientific, lot 007395): 0.02M potassium phosphate buffer (Sigma Aldrich, lot 90K0523, pH 3.0). All solvents were HPLC-grade and filtered before use. The flow rate was set at 1.2 mL/min.

A 5-point calibration curve was prepared with a blank (methanol) at the beginning of each run to ensure that there was no carry-over from one run to the next. The range of this calibration curve (0.031 to 0.05 mg/mL before dilution) encompasses the diluted concentrations of the 10 mg/mL and 1 mg/mL samples, respectively. The calibration curve was generated by least-squares regression of the ratio of the peak area of domperidone to that of propranolol versus the concentration of each standard solution. The precision of the assay was evaluated by intra-day and inter-day validation methods. Intra-day variation was determined by running 0.031, 0.125 and 0.250 mg/mL stock solutions (diluted to standards of 0.003, 0.0125, and 0.0250 mg/mL.) in quadruplicate throughout a single day, whereas the inter-day variation was determined by running the same concentrations (as in the testing for intra-day variation) in quadruplicate daily for 4 days. The means, standard deviations, and coefficients of variation were calculated. Acceptable limits for the coefficients of variation were defined *a priori* as less than 10%.

Degradation of Domperidone

Degradation of the drug was achieved as follows: domperidone (tablet 10mg/mL in methanol) was diluted 1:100 in water to a concentration of 0.1 mg/mL, and 0.5 mL hydrochloric acid 6N (Fisher Scientific, lot 299067) was added. This solution was incubated in a water bath at 95°C for 1 hour. Then, 0.5 mL of sodium hydroxide 10N (Fisher Scientific, lot SC9105042) was added and the solution was returned to the water bath at 95°C for 1 hour. After incubation, the solution was boiled for 15 minutes. The domperidone peak of the sample was compared to a standard (1 mg/mL) to determine changes in concentration, retention time, and peak shape.

Preparation of Samples

For each study sample, domperidone 1 mg/mL and 10 mg/mL were diluted to theoretical concentrations of 0.05 and 0.250 mg/mL, respectively. The diluted samples were centrifuged at 10,000 RPM for 5 min and then processed in a manner similar to that of the stock solutions. Each solution was passed through a 0.45- μ m microfilter before a 10-mL sample was withdrawn and injected onto the column.

Statistical Analysis

The means, standard deviations and coefficients of variation were calculated for samples analyzed in triplicate and quadruplicate. For each study day, the percentage of the initial domperidone concentration remaining was calculated for each sample. The percentage of domperidone remaining on day 91 was calculated from the concentration on day 91 as determined by linear regression and concentration observed on day zero, according to the following formula: concentration on day 91/concentration on day zero $\times$ 100. The 95% confidence interval (CI) of the amount remaining on the last study day was calculated from the lower limit of the 95% CI of the slope of the curve relating concentration to time, determined by linear regression, according to the following formula: lower limit of the 95% CI of the concentration on day 91/concentration on day zero $\times$ 100. Stability was determined as maintenance of at least 90% of the initial domperidone concentration.

Results

Regression analysis of the HPLC assay validation showed linearity over the working range of concentrations, with coefficients of determination (r^2) greater than 0.998 ($n=4$). The intra-day ($n=4$) and inter-day ($n=4$) coefficients of variation for the 3 different concentrations were within acceptable limits: 2.13% and 9.1%, respectively for the 0.031 mg/mL solution: 0.29% and 1.62%, respectively for the 0.125 mg/mL: 0.28% and 0.68%, respectively for the 0.250 mg/mL solution.

When domperidone was subjected to degradation, a major degradation product eluted at 1.48 min and one other minor degradation product could be detected at 2.7 min in the chromatogram (Figure 1). Neither of these products interfered with the quantification of the parent compound, domperidone.

No significant changes in physical appearance or odor of the suspensions were observed throughout the 91 days. Each cloudy white suspension had a faint sweet smell, maintained the same viscosity, and was easily resuspended throughout the study period. Furthermore, no significant fluctuations in pH were observed. The mean pH ($\pm$ standard deviation) was 4.27 ± 0.07 for the 1 mg/mL suspension stored at 25°C, 4.40 ± 0.09 for the 1 mg/mL suspension stored 4°C, 4.44 ± 0.06 for the 10 mg/mL suspension stored at 25°C, and 4.60 ± 0.10 for the 10 mg/mL suspension stored 4°C.

The retention time of domperidone was 2.2 minutes, while the retention time of the internal standard propranolol was 3.2 minutes (Figure 1). Results of the HPLC analysis show that at both storage temperatures, the 1 mg/mL and 10 mg/mL suspensions maintained at least 90% of their initial concentrations on every study day (Table 1). Furthermore, about 96% of the initial domperidone

concentration remained on day 91, according to linear regression analysis of the concentration-time data, and the lower limit of the 95% confidence interval indicated that more than 92% of the initial concentration remained on day 91 (Table 1).

Table I. Mean Domperidone Concentration $\pm$ Standard Deviation (and Mean Percentage Remaining^a) during 91 Days of Storage at 25°C and 4°C

Study Day	1 mg/mL ^b 25°C	1 mg/mL ^b 4°C	10 mg/mL ^b 25°C	10 mg/mL ^b 4°C
0	1.14 $\pm$ 0.045	1.10 $\pm$ 0.116	10.00 $\pm$ 0.65	10.53 $\pm$ 0.63
7	1.15 $\pm$ 0.18 (97.8%)	1.12 $\pm$ 0.06 (101.6%)	10.10 $\pm$ 1.18 (100.4%)	10.99 $\pm$ 0.44 (104.3%)
14	1.09 $\pm$ 0.12 (96.3%)	1.08 $\pm$ 0.07 (97.9%)	10.10 $\pm$ 0.38 (100.6%)	9.97 $\pm$ 0.20 (94.6%)
21	1.11 $\pm$ 0.23 (97.0%)	0.99 $\pm$ 0.04 (90.1%)	9.90 $\pm$ 0.66 (98.2%)	9.83 $\pm$ 1.73 (93.3%)
28	1.13 $\pm$ 0.24 (99.1%)	1.18 $\pm$ 0.20 (106.8%)	9.44 $\pm$ 0.87 (93.9%)	10.70 $\pm$ 0.46 (101.9%)
35	1.36 $\pm$ 0.04 (119.1%)	1.24 $\pm$ 0.10 (112.7%)	9.90 $\pm$ 1.93 (98.7%)	10.00 $\pm$ 2.11 (94.8%)
42	1.07 $\pm$ 0.08 (96.6%)	1.03 $\pm$ 0.24 (93.1%)	10.00 $\pm$ 0.34 (99.7%)	10.12 $\pm$ 0.69 (96.1%)
49	1.10 $\pm$ 0.20 (96.1%)	1.18 $\pm$ 0.26 (106.9%)	10.10 $\pm$ 0.76 (100.9%)	9.67 $\pm$ 0.47 (91.7%)
56	1.21 $\pm$ 0.22 (109.4%)	1.04 $\pm$ 0.25 (93.8%)	10.29 $\pm$ 1.05 (102.3%)	9.64 $\pm$ 1.06 (91.5%)
63	1.05 $\pm$ 0.12 (92.5%)	1.03 $\pm$ 0.29 (93.4%)	11.55 $\pm$ 0.36 (114.8%)	9.69 $\pm$ 0.90 (92.0%)
70	1.05 $\pm$ 0.26 (92.1%)	1.06 $\pm$ 0.16 (96.1%)	10.30 $\pm$ 0.66 (102.4%)	10.02 $\pm$ 1.20 (95.2%)
77	1.17 $\pm$ 0.31 (102.2%)	1.08 $\pm$ 0.23 (99.8%)	10.50 $\pm$ 0.14 (104.2%)	10.57 $\pm$ 0.19 (100.3%)
84	1.09 $\pm$ 0.02 (95.7%)	1.05 $\pm$ 0.11 (95.6%)	9.72 $\pm$ 0.52 (96.7%)	10.74 $\pm$ 0.92 (101.9%)
91	1.11 $\pm$ 0.05 (97.4%)	1.02 $\pm$ 0.12 (92.7%)	9.91 $\pm$ 1.14 (98.5%)	19.97 $\pm$ 1.78 (94.5%)
% remaining on day 91 ^c	103.93	106.55	96.32	102.68
Lower limit of 95% CI for % remaining ^d	92.75	94.49	93.78	93.17

CI = confidence interval

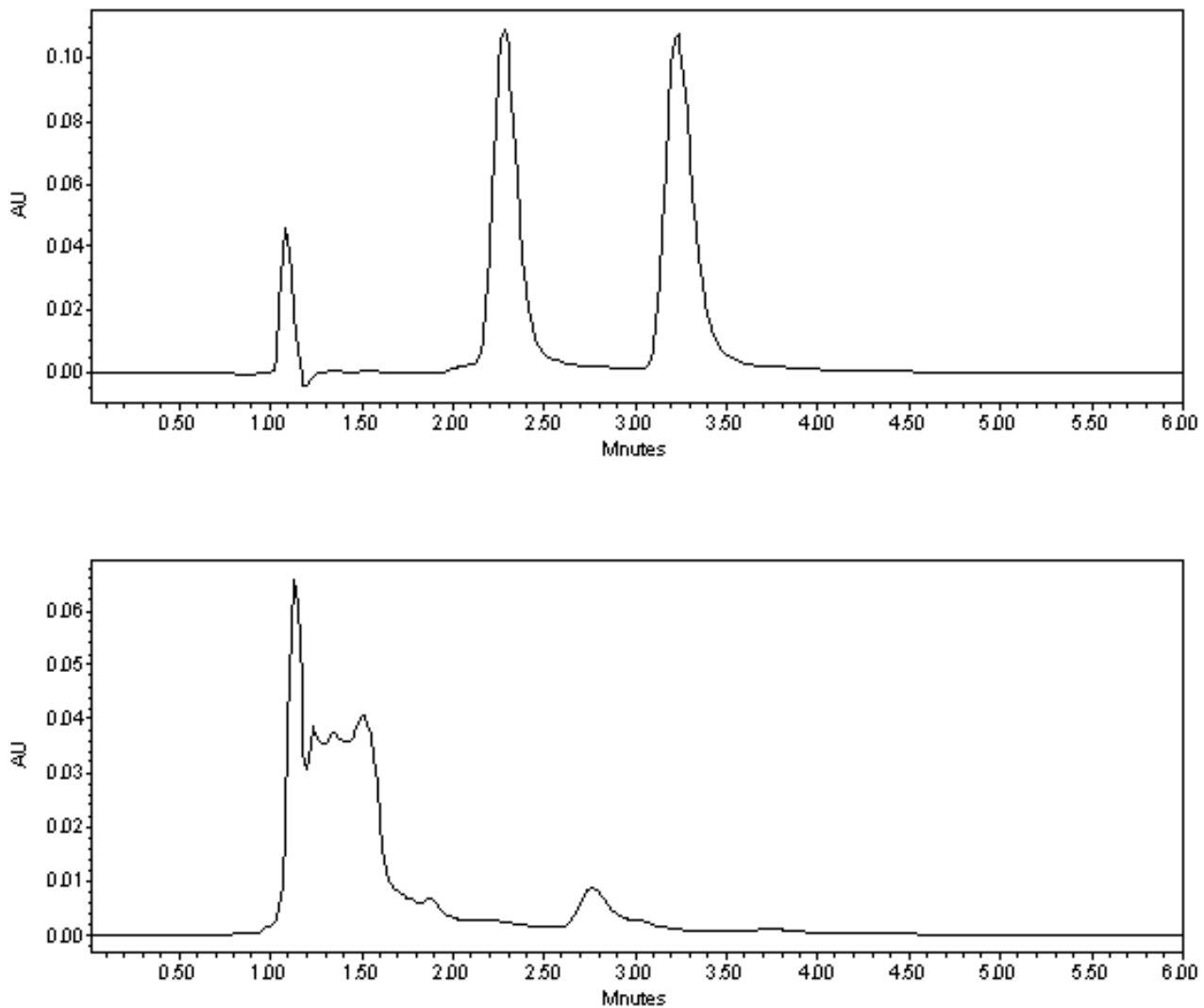
^aPercentage remaining was calculated in relation to the initial concentration (day zero)

^bNominal concentration

^cCalculated from concentration on day 91 as determined by linear regression and concentration observed on day zero, according to the following formula: concentration on day 91/concentration on day zero $\times$ 100.

^dCalculated from lower limit of 95% CI of the slope of the curve relating concentration to time, determined by linear regression, according to the following formula: lower limit of 95% CI of concentration on day 91/concentration on day zero $\times$ 100.

Figure 1: Upper panel: chromatogram showing domperidone peak at 2.2 min and the propranolol peak at 3.2 min. Lower panel: chromatogram of the degradation study showing degradation products at 1.48 and 2.7 min, respectively.



Discussion

Until the time of this study, domperidone suspension had been prepared at our institution in a methylcellulose vehicle. This product had an expiration date of only 8 days when kept refrigerated. To our knowledge, there are no published stability studies on domperidone suspension prepared in a 1:1 mixture of Ora-Sweet[®] and Ora-Plus[®].

In our weekly analysis of samples, color and odor changes were not noticeable, and samples were easily resuspended without caking, clumping, or crystal formation. Although these measures are qualitative, observations were documented by the same individual throughout the 91-day study period, thus eliminating potential inter-personnel bias. Variation in pH was not notable.

A limitation of this study design relates to the freezing of samples at -85°C until the time of batch analysis. It was assumed that domperidone would not degrade at this low temperature and that no volume losses would occur because of freeze-drying during storage. In addition, it was assumed that errors due to serial analysis would have been greater than any errors occurring with batch analysis. Furthermore, the variability in measured concentrations at various time points is greater than the assay's coefficients of variation and

suggests the need for the patient or caregiver to shake the suspension well before measuring each dose.

According to qualitative and HPLC analyses of weekly samples, domperidone suspensions of 1 mg/mL and 10 mg/mL stored at either 25°C or 4°C remained stable and maintained at least 90% of their original concentrations for up to 91 days. These results led to changes at our hospital for extemporaneous compounding of domperidone suspensions and the expiration date has been extended from 8 days to 3 months.

Funding Source

The study was supported by British Columbia's Children's Hospital Telethon Innovations Fund and the B.C. Research Institute of Child and Women's Health Investigator Establishment Award. Analytical-grade domperidone was provided as a gift from Apotex Inc.

Acknowledgement

The authors would like to acknowledge Mr. Paul M. Koke for his assistance in project logistics.

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Stability of Domperidone in Extemporaneously Compounded Suspensions

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Introduction: The recent withdrawal from the market of cisapride has prompted many practitioners to prescribe domperidone as the agent of first choice for patients requiring a gastrointestinal motility-enhancing agent. While domperidone is available in a solid dosage form (i.e. tablet) for oral use, pediatric and other patients who are unable to swallow tablets require an alternative dosage form.

Objectives: To evaluate the stability of 1 and 10 mg/mL domperidone suspensions in a vehicle consisting of equal parts of Ora-Sweet® and Ora-Plus® after storage at 25°C and 4°C for a maximum of 91 days.

Methods: Suspensions of domperidone 1 and 10 mg/mL, prepared from domperidone maleate tablets, were placed in 50 mL amber plastic bottles. Three bottles of each suspension were stored at 25°C (room temperature) and 3 were stored at 4°C (refrigerated). Physical characteristics including pH, color, odor, viscosity, precipitation, and ease of resuspension were observed weekly for 91 days. Aliquots were removed from each bottle weekly and stored at -85°C until analysis using a high performance liquid chromatography method. A suspension was considered stable if it maintained at least 90% of its initial concentration.

Results: No change in pH was observed in suspensions of either concentration after storage at 25°C or 4°C for 91 days. Changes in color and odor were not noticeable and viscosity was constant. Precipitates were easily resuspended and there was no caking or clumping of material. Suspensions of both concentrations of domperidone maintained at least 90% of initial concentration at both temperatures throughout the 91-day period.

Conclusions: Domperidone suspensions of both 1 and 10 mg/mL in a 1:1 mixture of Ora-Sweet® and Ora-Plus® were physically and chemically stable for a period of up to 91 days, both at room temperature and under refrigeration. The expiration date for these products can thus be set at 91 days.

J Inform Pharmacother 2002;8:100-104.

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A commercially-available vehicle (1:1 mixture of Ora-Sweet®:Ora-Plus®, a sweetening and suspending agent, respectively) has recently emerged as an alternative to methylcellulose. This newer vehicle eliminates many of the disadvantages associated with methylcellulose, since it is less labor-intensive, is available to both hospital and community pharmacies,

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and is consequently more convenient for outpatients. However, stability information for domperidone in Ora-Sweet[®]: Ora-Plus[®] does not currently exist.

This study involved an examination of the physical characteristics and chemical stability (defined as maintenance of more than 90% of initial concentration) of extemporaneously prepared oral domperidone suspensions of 1 and 10 mg/mL in a 1:1 mixture of Ora-Sweet[®] and Ora-Plus[®], stored at either 25°C or 4°C throughout a 91-day study period.

Methods

Preparation and Evaluation of Suspension

Domperidone suspensions (1 and 10 mg/mL) were prepared in triplicate from commercially-available tablets of domperidone maleate (Motilium[®], Novopharm, Scarborough, Ontario), containing domperidone 10 mg per tablet, and mixed with equal parts of Ora-Sweet[®] and Ora-Plus[®] (Paddock Laboratories Inc., Minneapolis, MN, lots OE6324 and OH6525, respectively). Six replicates of each concentration were prepared in separate 50-mL amber plastic prescription bottles, three of which were stored at 25°C (room temperature) and three at 4°C (refrigerated). All bottles were exposed only to the fluorescent lights in the laboratory.

Qualitative evaluation of physical appearance took place initially and at weekly intervals up to 91 days. All suspensions were visually examined (against white and black background), for color changes and precipitates, odor changes, layering, sedimentation, ease of resuspension, and gas formation. A fresh sample of each concentration was prepared and compared to a 1 mg/mL sample at 25°C, 1 mg/mL at 4°C, 10 mg/mL at 25°C and 10 mg/mL at 4°C for each of the original samples. Immediately following these physical observations, each suspension bottle was manually shaken for 10 seconds, pH was determined, and initial and weekly samples were removed and stored at -85°C until batch-analysis by a stability-indicating high performance liquid chromatography (HPLC) method.

Preparation of Stock and Standards

Stock solutions of domperidone at 0.50, 0.250, 0.125, 0.0625, and 0.0312 mg/mL were prepared by dilution of analytical-grade domperidone (Apotex Inc, Toronto, Ontario, lot X99207) in HPLC-grade methanol (Fisher Scientific, Richmond, British Columbia, lot 002129). The internal standard was propranolol (Sigma Aldrich, Oakville, Ontario, lot 90K0523) 0.250 mg/mL in HPLC-grade methanol. Standard solutions were prepared by further diluting a 0.1 mL aliquot of each stock solution and a 0.1 mL aliquot of propranolol 0.250 mg/mL to 1 mL with HPLC-grade methanol to obtain final concentrations of 0.05, 0.025, 0.0125, 0.0062, and 0.0031 mg/mL domperidone. This dilution step was necessary to achieve optimal chromatographics. Prior to injection, all standard solutions were passed through a 0.45-µm microfilter (Acrodisc GHP syringe filter, Gelman, Ann Arbor, Michigan, lot 5874) to prevent injection of impurities onto the column.

The HPLC instrumentation (model 2690, Waters Alliance System, Waters Ltd., Mississauga, Ontario) consisted of a delivery pump, an automatic injector equipped with a 200-µL injector, Nova Pak 3.9 x 20 mm guard column (Waters Ltd., lot W10721), a Nova-Pak C18 3.9 x 150 mm column (Waters Ltd., lot W02901M082), and an ultraviolet detector set at 205 nm (model 2487 dual-wavelength absorbance detector). The mobile phase was developed in the authors' laboratory and consisted of a 45:5:50 (v/v) mixture of methanol (Fisher Scientific, lot 002129): acetonitrile (Fisher Scientific, lot 007395): 0.02M potassium phosphate buffer (Sigma Aldrich, lot 90K0523, pH 3.0). All solvents were HPLC-grade and filtered before use. The flow rate was set at 1.2 mL/min.

A 5-point calibration curve was prepared with a blank (methanol) at the beginning of each run to ensure that there was no carry-over from one run to the next. The range of this calibration curve (0.031 to 0.05 mg/mL before dilution) encompasses the diluted concentrations of the 10 mg/mL and 1 mg/mL samples, respectively. The calibration curve was generated by least-squares regression of the ratio of the peak area of domperidone to that of propranolol versus the concentration of each standard solution. The precision of the assay was evaluated by intra-day and inter-day validation methods. Intra-day variation was determined by running 0.031, 0.125 and 0.250 mg/mL stock solutions (diluted to standards of 0.003,

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0.0125, and 0.0250 mg/mL.) in quadruplicate throughout a single day, whereas the inter-day variation was determined by running the same concentrations (as in the testing for intra-day variation) in quadruplicate daily for 4 days. The means, standard deviations, and coefficients of variation were calculated. Acceptable limits for the coefficients of variation were defined *a priori* as less than 10%.

Degradation of Domperidone

Degradation of the drug was achieved as follows: domperidone (tablet 10mg/mL in methanol) was diluted 1:100 in water to a concentration of 0.1 mg/mL, and 0.5 mL hydrochloric acid 6N (Fisher Scientific, lot 299067) was added. This solution was incubated in a water bath at 95°C for 1 hour. Then, 0.5 mL of sodium hydroxide 10N (Fisher Scientific, lot SC9105042) was added and the solution was returned to the water bath at 95°C for 1 hour. After incubation, the solution was boiled for 15 minutes. The domperidone peak of the sample was compared to a standard (1 mg/mL) to determine changes in concentration, retention time, and peak shape.

Preparation of Samples

For each study sample, domperidone 1 mg/mL and 10 mg/mL were diluted to theoretical concentrations of 0.05 and 0.250 mg/mL, respectively. The diluted samples were centrifuged at 10,000 RPM for 5 min and then processed in a manner similar to that of the stock solutions. Each solution was passed through a 0.45- μ m microfilter before a 10- μ L sample was withdrawn and injected onto the column.

Statistical Analysis

The means, standard deviations and coefficients of variation were calculated for samples analyzed in triplicate and quadruplicate. For each study day, the percentage of the initial domperidone concentration remaining was calculated for each sample. The percentage of domperidone remaining on day 91 was calculated from the concentration on day 91 as determined by linear regression and concentration observed on day zero, according to the following formula: concentration on day 91/concentration on day zero x 100. The 95% confidence interval (CI) of

the amount remaining on the last study day was calculated from the lower limit of the 95% CI of the slope of the curve relating concentration to time, determined by linear regression, according to the following formula: lower limit of the 95% CI of the concentration on day 91/concentration on day zero x 100. Stability was determined as maintenance of at least 90% of the initial domperidone concentration.

Results

Regression analysis of the HPLC assay validation showed linearity over the working range of concentrations, with coefficients of determination (r^2) greater than 0.998 ($n=4$). The intra-day ($n=4$) and inter-day ($n=4$) coefficients of variation for the 3 different concentrations were within acceptable limits: 2.13% and 9.1%, respectively for the 0.031 mg/mL solution: 0.29% and 1.62%, respectively for the 0.125 mg/mL: 0.28% and 0.68%, respectively for the 0.250 mg/mL solution.

When domperidone was subjected to degradation, a major degradation product eluted at 1.48 min and one other minor degradation product could be detected at 2.7 min in the chromatogram (Figure 1). Neither of these products interfered with the quantification of the parent compound, domperidone.

No significant changes in physical appearance or odor of the suspensions were observed throughout the 91 days. Each cloudy white suspension had a faint sweet smell, maintained the same viscosity, and was easily resuspended throughout the study period. Furthermore, no significant fluctuations in pH were observed. The mean pH ($\pm$ standard deviation) was 4.27 ± 0.07 for the 1 mg/mL suspension stored at 25°C, 4.40 ± 0.09 for the 1 mg/mL suspension stored 4°C, 4.44 ± 0.06 for the 10 mg/mL suspension stored at 25°C, and 4.60 ± 0.10 for the 10 mg/mL suspension stored 4°C.

The retention time of domperidone was 2.2 minutes, while the retention time of the internal standard propranolol was 3.2 minutes (Figure 1). Results of the HPLC analysis show that at both storage temperatures, the 1 mg/mL and 10 mg/mL suspensions maintained at least 90% of their initial concentrations on every study day (Table 1). Furthermore, about 96% of the initial domperidone

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concentration remained on day 91, according to linear regression analysis of the concentration-time data, and the lower limit of the 95% confidence interval indicated that more than 92% of the initial concentration remained on day 91.

Discussion

Until the time of this study, domperidone suspension had been prepared at our institution in a methylcellulose vehicle. This product had an expiration date of only 8 days when kept refrigerated. To our knowledge, there are no published stability studies on domperidone suspension prepared in a 1:1 mixture of Ora-Sweet® and Ora-Plus®.

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A limitation of this study design relates to the freezing of samples at -85°C until the time of batch analysis. It was assumed that domperidone would not degrade at this low temperature and that no volume losses would occur because of freeze-drying during storage. In addition, it was assumed that errors due to serial analysis would have been greater than any errors occurring with batch analysis.

Furthermore, the variability in measured concentrations at various time points is greater than the assay's coefficients of variation and suggests the need for the patient or caregiver to shake the suspension well before measuring each dose.

According to qualitative and HPLC analyses of weekly samples, domperidone suspensions of 1 mg/mL and 10 mg/mL stored at either 25°C or 4°C remained stable and maintained at least 90% of their original concentrations for up to 91 days. These results led to changes at our hospital for extemporaneous compounding of domperidone suspensions and the expiration date has been extended from 8 days to 3 months.

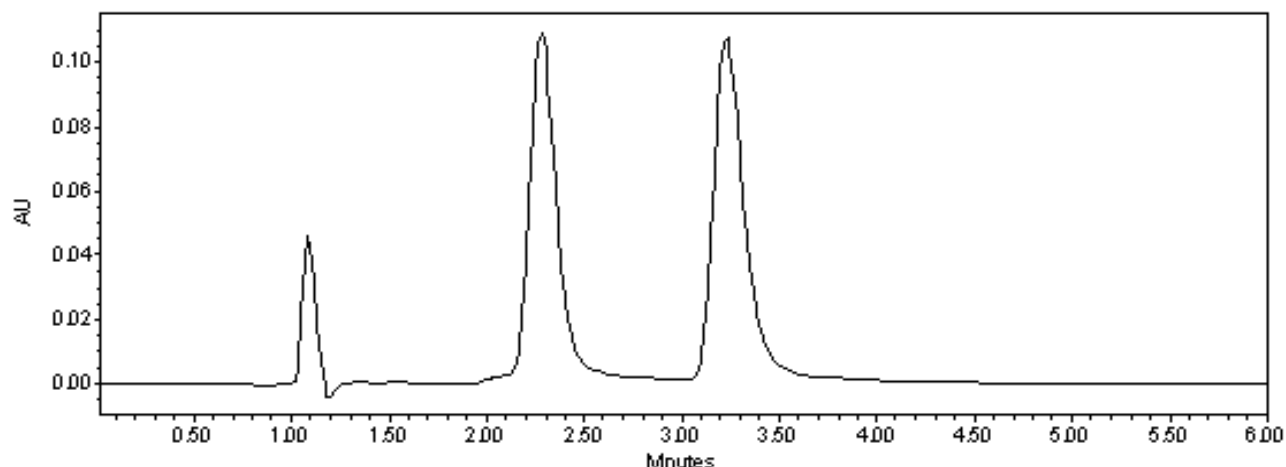
Funding Source

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Acknowledgement

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Figure 1: Upper panel: chromatogram showing domperidone peak at 2.2 min and the propranolol peak at 3.2 min. Lower panel: chromatogram of the degradation study showing degradation products at 1.48 and 2.7 min, respectively.



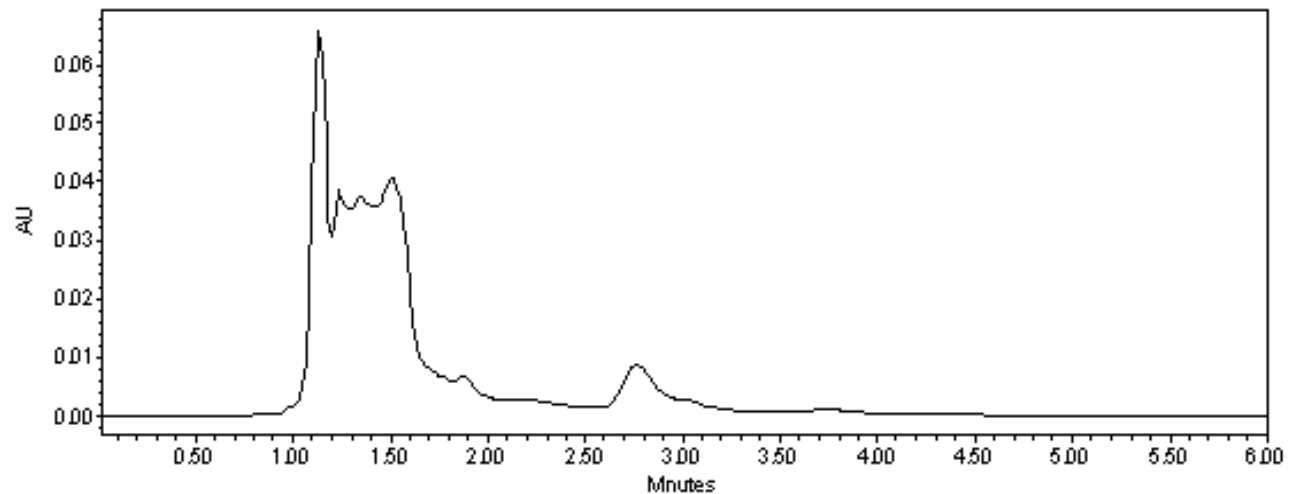


Table I. Mean Domperidone Concentration $\pm$ Standard Deviation (and Mean Percentage Remaining^a) during 91 Days of Storage at 25°C and 4°C

Study Day	1 mg/mL ^b 25°C	1 mg/mL ^b 4°C	10 mg/mL ^b 25°C	10 mg/mL ^b 4°C
0	1.14 $\pm$ 0.05	1.10 $\pm$ 0.12	10.00 $\pm$ 0.65	10.53 $\pm$ 0.63
7	1.15 $\pm$ 0.18 (97.8%)	1.12 $\pm$ 0.06 (101.6%)	10.10 $\pm$ 1.18 (100.4%)	10.99 $\pm$ 0.44 (104.3%)
14	1.09 $\pm$ 0.12 (96.3%)	1.08 $\pm$ 0.07 (97.9%)	10.10 $\pm$ 0.38 (100.6%)	9.97 $\pm$ 0.20 (94.6%)
21	1.11 $\pm$ 0.23 (97.0%)	0.99 $\pm$ 0.04 (90.1%)	9.90 $\pm$ 0.66 (98.2%)	9.83 $\pm$ 1.73 (93.3%)
28	1.13 $\pm$ 0.24 (99.1%)	1.18 $\pm$ 0.20 (106.8%)	9.44 $\pm$ 0.87 (93.9%)	10.70 $\pm$ 0.46 (101.9%)
35	1.36 $\pm$ 0.04 (119.1%)	1.24 $\pm$ 0.11 (112.7%)	9.90 $\pm$ 1.93 (98.7%)	10.00 $\pm$ 2.11 (94.8%)
42	1.07 $\pm$ 0.08 (96.6%)	1.03 $\pm$ 0.24 (93.1%)	10.00 $\pm$ 0.34 (99.7%)	10.12 $\pm$ 0.69 (96.1%)
49	1.10 $\pm$ 0.20 (96.1%)	1.18 $\pm$ 0.26 (106.9%)	10.10 $\pm$ 0.76 (100.9%)	9.67 $\pm$ 0.47 (91.7%)
56	1.21 $\pm$ 0.22 (109.4%)	1.04 $\pm$ 0.25 (93.8%)	10.29 $\pm$ 1.05 (102.3%)	9.64 $\pm$ 1.06 (91.5%)
63	1.05 $\pm$ 0.12 (92.5%)	1.03 $\pm$ 0.29 (93.4%)	11.55 $\pm$ 0.36 (114.8%)	9.69 $\pm$ 0.90 (92.0%)
70	1.05 $\pm$ 0.26 (92.1%)	1.06 $\pm$ 0.16 (96.1%)	10.30 $\pm$ 0.66 (102.4%)	10.02 $\pm$ 1.20 (95.2%)
77	1.17 $\pm$ 0.31 (102.2%)	1.08 $\pm$ 0.23 (99.8%)	10.50 $\pm$ 0.14 (104.2%)	10.57 $\pm$ 0.19 (100.3%)
84	1.09 $\pm$ 0.02 (95.7%)	1.05 $\pm$ 0.11 (95.6%)	9.72 $\pm$ 0.52 (96.7%)	10.74 $\pm$ 0.92 (101.9%)
91	1.11 $\pm$ 0.05 (97.4%)	1.02 $\pm$ 0.12 (92.7%)	9.91 $\pm$ 1.14 (98.5%)	19.97 $\pm$ 1.78 (94.5%)
% remaining on day 91 ^c	103.93	106.55	96.32	102.68
Lower limit of 95% CI for % remaining ^d	92.75	94.49	93.78	93.17

CI = confidence interval

^aPercentage remaining was calculated in relation to the initial concentration (day zero)

^bNominal concentration

^cCalculated from concentration on day 91 as determined by linear regression and concentration observed on day zero, according to the following formula: concentration on day 91/concentration on day zero $\times$ 100.

^dCalculated from lower limit of 95% CI of the slope of the curve relating concentration to time, determined by linear regression, according to the following formula: lower limit of 95% CI of concentration on day 91/concentration on day zero $\times$ 100

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"Fast Track" Evidence-Based Reviews

Due to the popularity of the **Evidence-Based Reviews of the Pharmacotherapy Literature** section, we are enhancing this section with more of what our readers want. JIP readers have told us that they want the "quick and dirty" on new trials that are reported virtually daily; Who was studied? What were the results? What does it mean? Our goal is to provide a synopsis of these studies **no later than one week** from the time it is released.

Individual section editors of JIP help us by suggesting studies they feel should be in this section. Our editors are experts in their therapeutic areas and review the journals pertinent to their expertise on a regular basis and we have asked them to identify studies they believe would be of interest to our readers. In particular, we are interested in those studies that have the potential to impact how we use pharmacotherapy or confirm in more detail what we already know. Experts in the area will also provide a brief commentary on the studies. We also invite you to **suggest articles which should appear in this section.**

It is not our goal to do a formal critical appraisal on each article but to create a simple synopsis of what was found. A more extensive critical review will continue to be done for selected studies in the **Evidence Based Reviews of the Pharmacotherapy Literature** section.

Evidence-Based Reviews of the Pharmacotherapy Literature

The purpose of Evidence-Based Reviews of the Pharmacotherapy Literature section is to alert clinicians to important advances in pharmacotherapy by selecting from the current biomedical literature those original and systematic review articles whose results are most likely to result in a change in clinical practice. These articles are summarized in structured abstracts and commented on by pharmacotherapy experts.

The procedures we follow as we attempt to achieve this purpose are:

1. Considering the best original and systematic review articles evaluating the clinical merit or economics of drug therapy.
2. Introducing these articles with declarative titles and summarizing them accurately in structured abstracts that follow the format for the User's Guide to the Medical Literature series originally published in JAMA by the Evidence Based Medicine Working Group.
3. Adding brief, highly expert commentaries to place each of these summaries in its proper clinical perspective.

4. Disseminating these summaries in a timely fashion to clinicians.

Journals are reviewed based on the proportion of articles that meet the following criteria:

Criteria for Acceptability for the Structured Abstract and Commentary

1. General: All English-language original and review articles are acceptable for abstracting if they concern topics important to the clinical practice of pharmacotherapy.

2. Studies of the clinical impact of drug therapy: random allocation of the participants to the different interventions; outcome measures of known or probable clinical importance for $\geq 80\%$ of the participants who entered the investigation. Reviewers of articles for this section should use the [on-line submission form](#) or the [printable form](#) based on the [User's Guide to the Medical Literature: How to Use an Article about Therapy or Prevention](#) (originally published in JAMA 1993;270(21):2598-601 & 1994;271(1):59-63).

3. Studies of the economics of drug therapy: The economic question must compare suitable alternative pharmacotherapeutic strategies; the alternative pharmacotherapeutic strategies must be compared on the basis of both the outcomes they produce (effectiveness) and the resources they consume (costs); evidence of effectiveness must come from a study (or studies) that meet the above criteria for an article on the clinical impact of drug therapy; results should be presented in terms of the incremental or additional costs and outcomes incurred and realized by one intervention over another; and a sensitivity analysis should be done. Reviewers of articles for this section should use the [on-line submission form](#) or the [printable form](#) based on the [User's Guide to the Medical Literature: How to Use an Economic Analysis of Clinical Practice](#) (originally published in JAMA 1997;277(19):1552-7 and 1997;278(13):1064).

4. Systematic reviews of the pharmacotherapy literature: The clinical topic being reviewed must be clearly stated; there must be a description of how the evidence on this topic was tracked down, from what sources, and with what inclusion and exclusion criteria; and ≥ 1 article included in the review must meet the above-noted criteria for the clinical impact or economics of drug therapy. Reviewers of articles for this section should use the [on-line submission form](#) or the [printable form](#) based on the [User's Guide to the Medical Literature: How to Use an Overview](#) (originally published in JAMA 1995;274(3):217-8).

For each article reviewed, a structured abstract (as described above) and a commentary should be provided. The commentary is added to provide the contexts of previous knowledge and clinical practice within which the results of the abstracted study apply, any important methodological problems that affect interpretation of the study results, and recommendations for the application of the study findings to the field of clinical pharmacotherapy. The commentary should not be longer than 400 words.

Are you a health care professional and would like to evaluate a pharmacotherapy article that impacts on clinical practice? Submit it to us for review!

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Please complete the form below to review an article on the Clinical Impact of Drug Therapy (e.g. a randomized controlled trial).

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Reviewer's Name:

Reviewer's E-mail address:

Reviewer's profession/specialty:

NAME OF ARTICLE:

JOURNAL REFERENCE

Fill in the fields below:

Overall Study Question: What were the objectives, the patient population, the outcome variables, and the interventions tested in this trial?

Comments:

I. Are the Results of the Study Valid?

1. Was the assignment of patients to treatment randomized?

Select one

Comments:

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Select one

Comments:

3. Were patients, their clinicians and study personnel 'blind' to treatment?

Select one

Comments:

4. Were the groups similar at the start of the trial?

Select one

Comments:

5. Aside from the experimental intervention, were the groups treated equally?

Select one

Comments:

II. What are the Results?

1. How large was the treatment effect?

Comments:

2. How precise was the estimate of the treatment effect?

Comments:

III. Will the results help me in caring for my patients?

1. Can the results be applied to my patients?

Select one

Comments:

2. Were all clinically important outcomes considered?

Select one

Comments:

3. Are the benefits worth the harms and costs?

Select one

Comments:

IV. How can the results be put into the context of previous knowledge and clinical practice? What are any important methodological issues with the study? How should the study findings be applied to the field of clinical pharmacotherapy?

Commentary:

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Citation:

After each main question, other questions have been added in smaller font to help guide your answers.

Overall Study Question:

What were the objectives, the patient population, the outcome variables, and the interventions tested in this trial?

Are the Results of the Study Valid?

1. Was assignment of randomized?

☐ Yes

- ☐ No
- ☐ Can't Tell

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion? - was

follow-up complete? - were patients analyzed in the groups to which they were randomized (intention to treat analysis)?

- ☐ Yes
- ☐ No
- ☐ Can't Tell

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

- ☐ Yes
- ☐ No
- ☐ Can't Tell

4. Were the groups similar at the start of the trial? Baseline prognostic factors (demographics, co-morbidity, disease severity, other known confounders) balanced? - If different, were these adjusted for?

- ☐ Yes
- ☐ No
- ☐ Can't Tell

5. Aside from the experimental intervention, were the groups treated equally? Co-intervention? Contamination?

Compliance?

- ☐ Yes
- ☐ No
- ☐ Can't Tell

6. Overall, are the results of the study valid?

☐ Yes

☐ No

☐ Can't Tell

What are the Results

1. How large was the treatment effect? Absolute risk reduction? Relative risk reduction?

2. How precise was the estimate of the treatment effect? Confidence intervals?

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care? Patients similar for demographics, severity, co-morbidity and other prognostic factors? Compelling reason why the results should not be applied?

☐ Yes

☐ No

☐ Can't Tell

2. Were all clinically important outcomes considered?

Are substitute endpoints valid?

☐ Yes

☐ No

☐ Can't Tell

3. Are the likely treatment benefits worth the potential harms and costs? NNT for different outcomes?

☐ Yes

☐ No

☐ Can't Tell

Commentary

- (to provide the contexts of previous knowledge and clinical practice within which the results of the abstracted study apply, any important methodological problems that affect interpretation of the study results, and recommendations for the application of the

study findings to the field of clinical pharmacotherapy)

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Fill in the fields below:

Overall Study Question: What were the objectives, the patient population, the outcome variables, and the interventions tested in this economic evaluation?

Comments:

I. Are the Results of the Study Valid?

1. Did the analysis provide a full economic comparison of health care strategies? (i.e. Costs and outcomes for each strategy? Whose viewpoint? Cost-effectiveness/benefit/utility study)?

Select one

Comments:

2. Were the costs and outcomes properly measured and valued? (i.e. Clinical effectiveness established? Costs measured accurately? Data on costs and outcomes appropriately integrated?)

Select one

Comments:

3. Was appropriate allowance made for uncertainties in the analysis? (i.e. Sensitivity analysis? Statistical significance?)

Select one

Comments:

4. Are estimates of costs and outcomes related to the baseline risk in the treatment population? (i.e. Sub-group analyses by risk?)

Select one

Comments:

II. What are the Results?

1. What were the incremental costs and outcomes of each strategy?

Comments:

2. Do incremental costs and outcomes differ between sub-groups?

Select one

Comments:

3. How much does allowance for uncertainty change the results?

Comments:

III. Will the results help me in caring for my patients?

1. Are the treatment benefits worth the harms and costs? (i.e. Strong dominance? Weak dominance? Non-dominance? Incremental cost-effectiveness?)

Select one

Comments:

2. Could my patients expect similar health outcomes? (i.e. Study patients similar to my patients? Study clinical management similar to my local practice?)

Select one

Comments:

3. Could I expect similar costs?(i.e. Study/local resource consumption similar?
Study/local costs similar?)

Select one

Comments:

IV. How can the results be put into the context of previous knowledge and clinical practice? What are any important methodological issues with the study? How should the study findings be applied to the field of clinical pharmacotherapy?

Commentary:

Clear

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Overall Study Question: What were the objectives, the patient population, the outcome variables, and the interventions tested in this economic evaluation?

Are the Results of the Study Valid?

1. Did the analysis provide a full economic comparison of health care strategies? Costs and outcomes for each strategy? Whose viewpoint? Cost-effectiveness/benefit/utility study?

- ☐ Yes
☐ No
☐ Can't Tell

2. Were the costs and outcomes properly measured and valued? Clinical effectiveness established? Costs measured accurately? Data on costs and outcomes appropriately integrated?

- ☐ Yes
- ☐ No
- ☐ Can't Tell

3. Was appropriate allowance made for uncertainties in the analysis? Sensitivity analysis? Statistical significance?

- ☐ Yes
- ☐ No
- ☐ Can't Tell

4. Are estimates of costs and outcomes related to the baseline risk in the treatment population? Sub-group analyses by risk?

- ☐ Yes
- ☐ No
- ☐ Can't Tell

What are the Results?

1. What were the incremental costs and outcomes of each strategy?

2. Do incremental costs and outcomes differ between sub-groups?

- ☐ Yes
- ☐ No
- ☐ Can't Tell

3. How much does allowance for uncertainty change the results?

Will the Results Help in Caring for My Patients?

1. Are the treatment benefits worth the harms and costs? Strong dominance? Weak dominance?

Non-dominance? Incremental cost-effectiveness?

- ☐ Yes
 - ☐ No
 - ☐ Can't Tell
-

2. Could my patients expect similar health outcomes? Study patients similar to my patients?

Study clinical management similar to my local practice?

☐ Yes

☐ No

☐ Can't Tell

3. Could I expect similar costs? Study/local resource consumption similar? Study/local prices

similar?

☐ Yes

☐ No

☐ Can't Tell

Commentary

- (to provide the contexts of previous knowledge and clinical practice within which the results of the abstracted study apply, any important methodological problems that affect interpretation of the study results, and recommendations for the application of the study findings to the field of clinical pharmacotherapy)

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JOURNAL REFERENCE

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Overall Study Question: What were the objectives, the patient population, the outcome variables, and the interventions tested in this systematic review?

Comments:

I. Are the Results of the Study Valid?

1. Did the overview address a focused clinical question?

Select one

2. Were the criteria used to select articles for inclusion appropriate?

Select one

Comments:

3. Is it unlikely that important, relevant studies were missed?

Select one

Comments:

4. Was the validity of the included studies appraised?

Select one

Comments:

5. Were assessments of studies reproducible?

Select one

Comments:

6. Were the results similar from study to study?

Select one

Comments:

II. What are the Results?

1. What are the overall results of the review?

Comments:

2. How precise were the results?

Comments:

3. How much does allowance for uncertainty change the results? (i.e. Sensitivity analysis? Analysis of

heterogeneity?)

Comments:

III. Will the results help me in caring for my patients?

1. Can the results be applied to my patient care?

Select one

Comments:

2. Were all clinically important outcomes considered?

Select one

Comments:

3. Are the benefits worth the harms and costs?

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Comments:

IV. How can the results be put into the context of previous knowledge and clinical practice? What are any important methodological issues with the study? How should the study findings be applied to the field of clinical pharmacotherapy?

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Overall Study Question: What were the objectives, the patient population, the outcome variables, and the interventions tested in this systematic review?

Are the Results of the Study Valid?

1. Did the overview address a focused clinical question?

- ☐ Yes
- ☐ No
- ☐ Can't Tell

2. Were the criteria used to select articles for inclusion appropriate?

- ☐ Yes
- ☐ No
- ☐ Can't Tell

3. Is it unlikely that important, relevant studies were missed?

- ☐ Yes
- ☐ No
- ☐ Can't Tell

4. Was the validity of the included studies appraised?

- ☐ Yes
- ☐ No
- ☐ Can't Tell

5. Were assessments of studies reproducible?

- ☐ Yes
- ☐ No
- ☐ Can't Tell

6. Were the results similar from study to study?

- ☐ Yes
 - ☐ No
 - ☐ Can't Tell
-

What are the Results?

1. What are the overall results of the review?

2. How precise were the results?

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

- ☐ Yes
☐ No
☐ Can't Tell
-

2. Were all clinically important outcomes considered?

- ☐ Yes
☐ No
☐ Can't Tell
-

3. Are the benefits worth the harms and costs?

- ☐ Yes
☐ No
☐ Can't Tell
-

Commentary

- (to provide the contexts of previous knowledge and clinical practice within which the results of the abstracted study apply, any important methodological problems that affect interpretation of the study results, and recommendations for the application of the study findings to the field of clinical pharmacotherapy)

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Last updated: March 27, 2000

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2002;8:200-202.

Academic Detailing in a Hospital Setting: Do Face-to-face Interactions influence Antibiotic Prescribing Behaviour?

Download a [PDF](#) version of this article

Reviewer: Terryn Naumann, B.Sc.(Pharm.), Pharm.D.

Reviewer's email address: tnaumann@interchange.ubc.ca

Reviewer's profession/specialty: Pharmacist - Academic detailing/Research

Original Citation

Soloman DH, Van Houten L, Glynn RJ, Badeb L, Curtis K, Schrager H, Avorn J. Academic detailing to improve antibiotic use of broad-spectrum antibiotics at an academic medical center. Arch Inter Med 2001; 161: 1897-1902. [PubMed Citation](#)

Overall Study Question

The objective of the study was to determine if a targeted one-on-one educational program ("academic detailing") by clinical specialists on a patient-specific basis could reduce excessive use of broad-spectrum antibiotics.

The study population consisted of the interns and residents who wrote antibiotic prescriptions for either levofloxacin or ceftazidime on 17 internal medicine services (9 general medicine, 4 oncology, and 4 cardiology) during a 18 week period. The educational intervention was directed at the interns and residents on the services in the intervention group who wrote "unnecessary" prescriptions for either levofloxacin or ceftazidime. A prescription was considered unnecessary if it fell outside the guidelines for appropriate use developed by the hospital's Division of Infectious Diseases. One of the 3 clinical educators (2 Infectious Disease physicians and 1 clinical pharmacist) contacted the prescribing intern or resident to arrange a face-to-face meeting. Using an academic detailing approach, the clinical educator would present information in a case-relevant, concise manner, stressing microbiological data, local resistance patterns, and the clinical literature. The educator would suggest alternative regimens, but the final choice was left to the intern or resident. The educational sessions lasted approximately 10 minutes.

The primary outcome variable was to compare the average number of days of unnecessary levofloxacin

and ceftazidime use during each 2-week period for the intervention and control services. Secondary outcome variables included examining the medication prescriptions for the day of the educational intervention and the subsequent day to determine if the unnecessary antibiotic was continued, discontinued or changed in route or dosage. Length of stay, proportion of patients transferred to ICU, readmitted within 30 days, or died in hospital were also compared for every patient admitted to an intervention or control service during the study period.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Seventeen services were assigned to intervention or control group status using a blocked randomization design to achieve balanced patient groups. Five general medicine, 2 oncology, and 2 cardiology services were included in the intervention group. Four general medicine, 2 oncology, and 2 cardiology services made up the control group.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

During the 18-week study period, 490 patients from all study services were prescribed levofloxacin or ceftazidime. Computerized records indicated that 212 patients did not meet the criteria for 'unnecessary' use and were excluded. The remaining 278 prescriptions in 260 patients were flagged as unnecessary (125 in the intervention services and 153 in the control services). In 14 instances, the clinical educator decided not to contact the prescribing intern or resident after reviewing the patient's chart. This was typically due to the fact that the previous Infectious Disease consultant had recommended one of the targeted antibiotics. These prescriptions were included in all analyses.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

No. The interns and residents were not aware that their prescribing practices were being studied. While the clinical educators were unblinded, the initial screening criteria to identify unnecessary prescriptions were applied without regard to study group assignment.

4. Were the groups similar at the start of the trial?

Patient characteristics (admissions per 2 week period, patient age and gender) were similar on the intervention and control services and did not differ during baseline and study periods. There were slightly higher rates of fever and neutropenia among patients prescribed levofloxacin on the intervention services during the study period.

5. Aside from the experimental intervention, were the groups treated equally?

The intervention and control services were treated equally. The study hospital's Division of Infectious Diseases developed a set of guidelines for first line antibiotic therapy including recommendations for the proper use of levofloxacin and ceftazidime. All house staff received a pocket sized laminated brochure of the guidelines prior to the study. The possibility of contamination between intervention and control groups exists as residents switch services every month. This would have been expected to bias the results against finding a difference or towards finding less of an effect.

What were the Results?

1. How large was the treatment effect?

During the baseline period, the mean number of days of unnecessary levofloxacin or ceftazidime use in a 2-week period was not different between the intervention and control services (8.5 +/- 7.8 days versus 7.6 +/- 4.7 days). During the study period, the intervention services had 5.5 +/- 2.1 days of unnecessary antibiotics versus 8.8 +/- 2.2 days on the control services (a relative reduction of 37%, $p < 0.001$) as a result of 28 fewer starts, and a 0.8 day shorter average antibiotic course.

On the intervention services, 70% of the unnecessary prescriptions were discontinued the next day versus only 30% on the control services. Also, 55% of the patients on the intervention services had all of their antibiotics discontinued versus only 16% on control services. Route changes were equal and relatively uncommon on both services (14%).

2. How precise was the estimate of the treatment effect?

A multivariate analysis done to account for repeated measures of target antibiotics and baseline prescribing indicated that the risk of receiving a day of unnecessary levofloxacin or ceftazidime was reduced by 41% (CI: 44-78%) on the intervention services compared with control.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

The relative success of 'academic detailing' is dependent upon the ability and the availability of the clinical educator. This study used 2 Infectious Disease physicians and 1 clinical pharmacist as their clinical educators. While many hospitals do not have an Infectious Disease Consult Service, or have physicians available to perform academic detailing, most hospitals have clinical pharmacists who routinely review the use of broad spectrum antibiotics on a patient-specific basis and consult with the prescribing physician when an alternative antibiotic may be more appropriate. While this paper does not differentiate between the effectiveness of the clinical educators, the authors mention that the impact of the clinical pharmacist was similar to that of the Infectious Disease physicians.

2. Were all clinically important outcomes considered?

All clinically important outcomes were considered.

3. Are the likely treatment benefits worth the potential harms and costs?

The benefit of the academic detailing sessions was a decrease in the use of the targeted broad-spectrum antibiotics, levofloxacin and ceftazidime, with no measurable harmful effect. There was no difference in length of stay, proportion of patients transferred to ICU, readmitted within 30 days, or death rates between the 2 services. In addition, decreased use of these broad-spectrum agents should reduce the risk of antibiotic resistance associated with overuse of broad-spectrum antibiotics.

Commentary

This is the first study to formally evaluate the effectiveness of academic detailing in a hospital setting. Previous studies involving academic detailing have primarily focused on altering prescribing practices in the community or residential care settings. This study reinforces the value of using a brief, face-to-face interaction with evidence-based information as an effective method for modifying prescribing practices.

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Academic Detailing in a Hospital Setting: Do Face-to-face Interactions influence Antibiotic Prescribing Behaviour?

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Reviewer's profession/specialty: Pharmacist - academic detailing/research

Original Citation

Soloman DH, Van Houten L, Glynn RJ, Badeb L, Curtis K, Schrager H, Avorn J. Academic detailing to improve antibiotic use of broad-spectrum antibiotics at an academic medical center. *Arch Inter Med* 2001; 161: 1897-1902..

Overall Study Question

The objective of the study was to determine if a targeted one-on-one educational program ("academic detailing") by clinical specialists on a patient-specific basis could reduce excessive use of broad-spectrum antibiotics.

The study population consisted of the interns and residents who wrote antibiotic prescriptions for either levofloxacin or ceftazidime on 17 internal medicine services (9 general medicine, 4 oncology, and 4 cardiology) during a 18 week period. The educational intervention was directed at the interns and residents on the services in the intervention group who wrote "unnecessary" prescriptions for either levofloxacin or ceftazidime. A prescription was considered unnecessary if it fell outside the guidelines for appropriate use developed by the hospital's Division of Infectious Diseases. One of the 3 clinical educators (2 Infectious Disease physicians and 1 clinical pharmacist) contacted the prescribing intern or resident to arrange a face-to-face meeting. Using an academic detailing approach, the clinical educator would present information in a case-relevant, concise manner, stressing microbiological data, local resistance patterns, and the clinical literature. The educator

would suggest alternative regimens, but the final choice was left to the intern or resident. The educational sessions lasted approximately 10 minutes.

The primary outcome variable was to compare the average number of days of unnecessary levofloxacin and ceftazidime use during each 2-week period for the intervention and control services. Secondary outcome variables included examining the medication prescriptions for the day of the educational intervention and the subsequent day to determine if the unnecessary antibiotic was continued, discontinued or changed in route or dosage. Length of stay, proportion of patients transferred to ICU, readmitted within 30 days, or died in hospital were also compared for every patient admitted to an intervention or control service during the study period.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Seventeen services were assigned to intervention or control group status using a blocked randomization design to achieve balanced patient groups. Five general medicine, 2 oncology, and 2 cardiology services were included in the intervention group. Four general medicine, 2 oncology, and 2 cardiology services made up the control group.

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2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

During the 18-week study period, 490 patients from all study services were prescribed levofloxacin or ceftazidime. Computerized records indicated that 212 patients did not meet the criteria for 'unnecessary' use and were excluded. The remaining 278 prescriptions in 260 patients were flagged as unnecessary (125 in the intervention services and 153 in the control services). In 14 instances, the clinical educator decided not to contact the prescribing intern or resident after reviewing the patient's chart. This was typically due to the fact that the previous Infectious Disease consultant had recommended one of the targeted antibiotics. These prescriptions were included in all analyses.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

No. The interns and residents were not aware that their prescribing practices were being studied. While the clinical educators were unblinded, the initial screening criteria to identify unnecessary prescriptions were applied without regard to study group assignment.

4. Were the groups similar at the start of the trial?

Patient characteristics (admissions per 2 week period, patient age and gender) were similar on the intervention and control services and did not differ during baseline and study periods. There were slightly higher rates of fever and neutropenia among patients prescribed levofloxacin on the intervention services during the study period.

5. Aside from the experimental intervention, were the groups treated equally?

The intervention and control services were treated equally. The study hospital's Division of Infectious Diseases developed a set of guidelines for first line antibiotic therapy including recommendations for the proper use of levofloxacin and ceftazidime. All house staff received a pocket sized laminated brochure of the guidelines prior to the study. The possibility of contamination between intervention and control groups exists as residents switch services every month. This would have been expected to bias the results against finding a difference or towards finding less of an effect.

What were the Results?

1. How large was the treatment effect?

During the baseline period, the mean number of days of unnecessary levofloxacin or ceftazidime use in a 2-week period was not different between the intervention and control services (8.5 +/- 7.8 days versus 7.6 +/- 4.7 days). During the study period, the intervention services had 5.5 +/- 2.1 days of unnecessary antibiotics versus 8.8 +/- 2.2 days on the control services (a relative reduction of 37%, $p < 0.001$) as a result of 28 fewer starts, and a 0.8 day shorter average antibiotic course.

On the intervention services, 70% of the unnecessary prescriptions were discontinued the next day versus only 30% on the control services. Also, 55% of the patients on the intervention services had all of their antibiotics discontinued versus only 16% on control services. Route changes were equal and relatively uncommon on both services (14%).

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Will the Results Help Me in Caring for My Patients? Commentary

1. Can the results be applied to my patient care?

The relative success of 'academic detailing' is dependent upon the ability and the availability of the clinical educator. This study used 2 Infectious Disease physicians and 1 clinical pharmacist as their clinical educators. While many hospitals do not have an Infectious Disease Consult Service, or have physicians available to perform academic detailing, most hospitals have clinical pharmacists who routinely review the use of broad spectrum antibiotics on a patient-specific basis and consult with the prescribing physician when an alternative antibiotic may be more appropriate. While this paper does not differentiate between the effectiveness of the clinical educators, the authors mention that the impact of the clinical pharmacist was similar to that of the Infectious Disease physicians.

2. Were all clinically important outcomes considered?

All clinically important outcomes were considered.

3. Are the likely treatment benefits worth the potential harms and costs?

The benefit of the academic detailing sessions was a decrease in the use of the targeted broad-spectrum antibiotics, levofloxacin and ceftazidime, with no measurable harmful effect. There was no difference in length of stay, proportion of patients transferred to ICU, readmitted within 30 days, or death rates between the 2 services. In addition, decreased use of these broad-spectrum agents should reduce the risk of antibiotic resistance associated with overuse of broad-spectrum antibiotics.

This is the first study to formally evaluate the effectiveness of academic detailing in a hospital setting. Previous studies involving academic detailing have primarily focused on altering prescribing practices in the community or residential care settings. This study reinforces the value of using a brief, face-to-face interaction with evidence-based information as an effective method for modifying prescribing practices.

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2002;8:203-205.

Who Should Receive Phytonadione (Vitamin K1) for Excessive Warfarin Anticoagulation?

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Reviewer's profession/specialty: Research Coordinator, Pharmacy Department/Cardiovascular Pharmacotherapy

Original Citation

Hylek EM, Regan S, Go AS, Hughes RA, Singer DE, Skates SJ. Clinical predictors of prolonged delay in return of the international normalized ratio to within the therapeutic range after excessive anticoagulation with warfarin. Ann Intern Med 2001;135:393-400. [PubMed Citation](#)

Overall Study Question

The objective of this study was to identify predictors of the rate of INR normalization after excessive warfarin anticoagulation. The authors suggest this information would be useful for identifying patients who should receive phytonadione (vitamin K1); namely, those patients at high risk for prolonged excessive anticoagulation for whom aggressive intervention is warranted. This information might also be used to identify patients who could safely forgo treatment with phytonadione, thus avoiding the possibility of increased thromboembolic risk through over-correction of INR.

These authors have published previous research on anticoagulation including a widely quoted article identifying acetaminophen as a risk factor for excessive anticoagulation with warfarin (1). For the current study, they have used a similar study design and drawn upon the same patient population, namely those patients attending their anticoagulation clinic. All patients attended the clinic between 1993 and 1998, had an INR greater than 6.0, two subsequent warfarin doses held, were interviewed within 24 hours of their elevated INR, and had a follow-up INR on the second calendar day. Patients whose INR was <4.0 on day 2 were compared to those whose INR was >4 on day 2. Variables evaluated as potential risk factors for INR >4 included age, warfarin dose, recently started medications, concurrently illness, decreased oral intake, confusion about their warfarin dose, non-adherence, hospitalization, and increased alcohol intake. Data was obtained through review of clinical and hospital

records.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

No. This was a retrospective, cohort study.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Of the 7279 managed in the study centre during the study period, 1995 had at least one INR >6.0. Of these, 639 met the inclusion criteria. Six patients were excluded: five because they had received phytonadione within the first 48 hours and one with hepatitis. Of the 633 patients included in the analysis, nursing notes on alcohol consumption, oral intake and new medications were missing for 21 patients (3%). There was no explanation of how the missing data was handled in the analysis.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

No. This was a retrospective, cohort study, therefore blinding was not possible.

4. Were the groups similar at the start of the trial?

No. There were significant differences in several variables between those patients with INR <4.0 and those with an INR >4.0 on day 2. The objective of this study was to identify these differences.

5. Aside from the experimental intervention, were the groups treated equally?

There was no experimental intervention in this study.

What were the Results?

1. How large was the treatment effect and how precise was the estimate of this effect?

Of the 633 study patients, 232 (37%) had an INR >4.0 after two doses of warfarin were withheld (i.e. on day 2). Independent risk factors for elevated INR on day 2 were older age (OR 1.18 per decade, 95% CI 1.01 – 1.38, p=0.04), higher index INR (OR 1.25 per unit

increase, 95% CI 1.14-1.37, $p < 0.001$), decompensated congestive heart failure (OR 2.79, 95% CI 1.30-5.98, $p = 0.009$), and active cancer (OR 2.48, 95% CI 1.11-5.57, $p = 0.03$). Higher weekly warfarin dose was associated with a lower odds of an elevated INR on day 2 (OR 0.87 per 10 mg increase, 95% CI 0.79-0.97, $p = 0.009$). The authors also present results of model-generated probabilities of the combined effects of these risk factors with several hypothetical examples. For example, a 60 year old patient taking 57.5 of warfarin per week has a model-generated probability of 14% for an INR > 4.0 on day 2, while an 80 year old taking 42.5 mg/week has nearly three times the risk (40%).

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

The authors suggest that their results help identify patients for whom early treatment with phytonadione to correct excessive warfarin anticoagulation is warranted. Since this is a commonly encountered clinical dilemma with serious potential consequences, information which helps clarify this decision will be valuable in clinical practice. However, the effects of administering or withholding phytonadione in specific patients was not directly studied. While the identified risk factors for excessive anticoagulation should be evaluated when deciding whether phytonadione administration is appropriate, other patient factors should also be considered (see below).

2. Were all clinically important outcomes considered?

Warfarin anticoagulation is highly variable and can be influenced by a wide variety of factors. There are hundreds of potential pharmacokinetic and pharmacodynamic variables to consider. Therefore, it would be neither technically feasible nor statistically appropriate to attempt to account for all potentially important variables in a regression model where the objective is to identify risk factors for excessive anticoagulation.

Hylek et al. have included a relatively large number of patients with outcome of interest in their analysis allowing them to evaluate a considerable number of variables without compromising model stability (a maximum of 10 patients with events per variable has been proposed). (2) However, there is sparse information about the statistical methods use to build and test the model. Therefore, there is some doubt whether accepted steps in regression model analysis; such as testing for interactions between variables, testing for co-linearity, and considering outliers; were carried out. (3)

This study was carried out at one site, and the model was not validated in another patient sample, therefore the risk factors identified here may not be applicable to patients in other settings. Furthermore, data was collected exclusively from historical records raising questions about the accuracy and thoroughness of the data used in the analysis. For example, there is no explanation of how information about medication use and adherence was documented in the clinic records, or the period over which patients were expected to recall relevant exposures. Patient recall is often incomplete or inaccurate, which may have lead to an underestimation of the risk associated with some

of the variables evaluated (e.g. alcohol consumption or specific medications).

It is interesting to consider that Hylek's earlier study on risk factors for excessive warfarin anticoagulation identified "newly started potentiating medication" as a strong risk factor (OR 8.5, 95% CI 2.9-24.7, $p < 0.001$), while medications did not appear to have a significant independent effect in this more recent study.

Finally, other potentially important risk factors were not considered including adherence with concurrent potentiating medications or the use of alternative medicines.

3. Are the likely treatment benefits worth the potential harms and costs?

There was no intervention in this study to evaluate potential harm versus potential benefit. If one is considering the harm versus benefit of administering phytonadione to a warfarin patient with an elevated INR, then the limitations of this study outlined above should be considered.

Commentary

Even with the limitations of this study outlined above, the risk factors identified are likely important in many patients taking warfarin, and should be considered when evaluating the need for phytonadione administration in patients with elevated INR results. The authors suggest that elderly patients taking low doses of warfarin (<15 mg/week), especially those with cancer or decompensated congestive heart failure, should receive early phytonadione administration to limit the chance of major hemorrhage. Conversely, they claim that the risk of intervention with phytonadione probably outweighs the benefit for younger patients with warfarin doses exceeding 50mg per week. However, an accompanying editorial suggests that the most recent guidelines for phytonadione administration limit the chance of over correction of the INR 4.

Given the complexity of warfarin pharmacodynamics, it is particularly important to evaluate each patient's need for phytonadione based on their individual characteristics and exposures. The risk factors identified in this study may not be the most important issues to consider for many patients encountered in your clinical practice.

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Who Should Receive Phytonadione (Vitamin K1) for Excessive Warfarin Anticoagulation?

Reviewer: Stephen Shalansky, Pharm.D., FCSHP

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Reviewer's profession/specialty: Research Coordinator, Pharmacy Department/Cardiovascular Pharmacotherapy

Original Citation

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of their elevated INR, and had a follow-up INR on the second calendar day. Patients whose INR was <4.0 on day 2 were compared to those whose INR was >4 on day 2. Variables evaluated as potential risk factors for INR >4 included age, warfarin dose, recently started medications, concurrently illness, decreased oral intake, confusion about their warfarin dose, non-adherence, hospitalization, and increased alcohol intake. Data was obtained through review of clinical and hospital records.

Are the Results of the Study Valid?

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2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Of the 7,279 managed in the study centre during the study period, 1,995 had at least one INR >6.0 . Of these, 639 met the inclusion criteria. Six patients were excluded: five because they had received phytonadione within the first 48 hours and one with hepatitis. Of the 633 patients included in the analysis, nursing notes on alcohol consumption, oral intake and new medications were missing for 21 patients (3%). There was no explanation of how the missing data was handled in the analysis.

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1. How large was the treatment effect and how precise was the estimate of this effect?

Of the 633 study patients, 232 (37%) had an INR >4.0 after two doses of warfarin were withheld (i.e. on day 2). Independent risk factors for elevated INR on day 2 were older age (OR 1.18 per decade, 95% CI 1.01 - 1.38, $p=0.04$), higher index INR (OR 1.25 per unit increase, 95% CI 1.14-1.37, $p<0.001$), decompensated congestive heart failure (OR 2.79, 95% CI 1.30-5.98, $p=0.009$), and active cancer (OR 2.48, 95% CI 1.11-5.57, $p=0.03$). Higher weekly warfarin dose was associated with a lower odds of an elevated INR on day 2 (OR 0.87 per 10 mg increase, 95% CI 0.79-0.97, $p=0.009$). The authors also present results of model-generated probabilities of the combined effects of these risk factors with several hypothetical examples. For example, a 60 year old patient taking 57.5 of warfarin per week has a model-generated probability

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Commentary

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Given the complexity of warfarin pharmacodynamics, it is particularly important to evaluate each patient's need for phytonadione based on their individual characteristics and exposures. The risk factors identified in this study may not be the most important issues to consider for many patients encountered in your clinical practice.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2002;8:206-209.

Type 1 Diabetes Mellitus and Microalbuminuria: Should All Patients Receive ACE inhibitors?

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Reviewer's profession/specialty: University of British Columbia Pharm.D. student (JW), Dialysis Pharmacist/Residency Coordinator (KS)

Original Citation

The ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. Ann Intern Med 2001;134:370-379. [PubMed Citation](#)

Overall Study Question

The effectiveness of angiotensin-converting enzyme (ACE) inhibitors in reversing and/or preventing progression of microalbuminuria in patients with type 1 diabetes mellitus (DM) is already well-established. (1,2,3) Using the rate of change of albumin excretion rate (AER) as the primary outcome measure, the main objective of this meta-analysis was to determine if there was a subgroup of patients with type 1 DM and microalbuminuria who were most likely to benefit from ACE inhibitor therapy. The subgroups identified included age, duration of diabetes, gender and glycemic control (hemoglobin A1c). The investigators also examined the impact of blood pressure (BP) and baseline AER as covariates on treatment effect. Finally, the risk for progression to macroalbuminuria and regression to normoalbuminuria was also examined.

Are the Results of the Study Valid?

1. Did the overview address a focused clinical question?

The authors could have been more explicit in phrasing their clinical questions, and could have expressed their objectives in a more concise form. They did not delineate a priori

all covariates to be considered in their objectives.

2. Were the criteria used to select articles for inclusion appropriate?

Yes. Criteria for study selection included trials with at least 10 patients who had: 1) type 1 DM; 2) normotension, as defined by each individual trial; and 3) microalbuminuria, as defined as an AER of 20-200 mcg/min measured at baseline and one or more follow-up visits. All trials were required to have a placebo or non-intervention group, and a minimum follow up of 1 year. Of note, one-third of the patients who were classified as normotensive in earlier studies were actually considered hypertensive by current standards. This variance, however, allowed the authors to observe the efficacy of ACE inhibitors over a wider range of blood pressures. Other antihypertensive medication that patients may have been taking other than ACE inhibitors were never mentioned by the authors.

3. Is it unlikely that important, relevant studies were missed?

Probably. Only one database (Medline) was employed, thus studies not indexed in this database may have been missed. However, bibliographies of published studies were also reviewed by the authors, and experts in the field were also consulted. Manufacturers or trial registries did not appear to have been contacted by the authors, and no information was provided to suggest that abstracts from conference proceedings were reviewed. The authors also did not specify any restrictions on their searching (i.e. years considered or languages of publication).

4. Was the validity of the included studies appraised?

No. Information was not provided on how many reviewers were involved in retrieving the studies or assessing these studies for inclusion or exclusion from the meta-analysis. The reviewers did not comment on whether or not they were blind to study results when studies were selected for inclusion.

5. Were assessments of studies reproducible?

This meta-analysis assessed raw data obtained from all trials and pooled them to create one large database. Trial investigators were contacted to obtain individual patient data with respect to the objectives of this study. This method was employed as the authors claimed that individual studies were underpowered to analyze for subgroup effects or risk for progression to macroalbuminuria. As well, analysis of individual patient data allowed a consistent approach to assess renal outcome (ie. AER), covariates, and subgroup effects.

Both a trial-level and a patient-level analysis was performed. For the trial-level analysis, both

fixed-effects and random-effects models were used to provide an estimate of the treatment effect, and estimates of between-trial variance were calculated. Treatment effect was expressed as a percentage difference of the relative change in AER between treatment and control groups compared to baseline. For the patient-level analysis, a random-effects regression model was used to determine the treatment effect for each patient. The authors do not state whether certain baseline risk factors (e.g. age, diabetes duration) were analyzed as continuous or categorical variables to determine a possible interaction.

Progression to macroalbuminuria or regression to normoalbuminuria may not have been as reproducible. Macroalbuminuria and normoalbuminuria were defined as AER greater than 200mcg/min or less than 20mcg/min, respectively, on two successive occasions at least 3 months apart, or at final visit. Since some patients may have met the criteria upon their final visit, the durability of the result over time could not be assessed.

6. Were the results similar from study to study?

All trials with at least a 2-year follow-up (n=10) showed a beneficial effect of ACE-inhibitors on rate of change in AER.

What were the Results?

1. What are the overall results of the review?

Initially, 12 trials and 698 patients were included in the meta-analysis. However, final analysis of treatment effects was limited to those studies with at least 2 years of follow-up, effectively excluding 2 trials and resulting in a total of 646 patients.

ACE inhibitors used in the trials were captopril (3 trials), lisinopril (3 trials), ramipril (2 trials), enalapril (1 trial) and perindopril (1 trial). Overall, at two years and using a random-effects model, AER was 50.2% (95% CI, 30.0%-64.6%, $p<0.001$) lower in patients receiving ACE inhibitors as compared to placebo. When the impact of a reduction in blood pressure on AER was accounted for, the treatment effect was attenuated slightly to 45.1% ($p<0.001$). A more pronounced reduction in AER was noted among subjects who had a baseline AER at the upper end of microalbuminuria (200 mcg/min) compared to those at the lower end (20 mcg/min) (74.1% vs. 17.8%, respectively, $p=0.04$). Other covariates (age, diabetes duration, sex, glycemic control) had no apparent impact on treatment effect.

Progression to macroalbuminuria decreased by one-third as compared to placebo, with an odds ratio (OR) of 0.38 (95% CI, 0.25-0.57, $p<0.001$) in favour of the ACE inhibitor. As well, there was a threefold increase in regression to normoalbuminuria with an OR of 3.07 (95% CI, 2.15-4.44, $p<0.001$). All trials demonstrated beneficial effects of ACE inhibitors with respect to regression to normoalbuminuria, and all were favourable except for one

regarding risk for progression to macroalbuminuria.

2. How precise were the results?

Both fixed-effects and random-effects models showed similar results on rate of change of AER. A marginal attenuation in treatment effect was observed using the estimates derived from the patient-level rather than trial-level regression models. The confidence intervals around the treatment estimate for the progression to macroalbuminuria and the regression to normoalbuminuria were fairly narrow. The lower boundary of both confidence intervals (0.25 and 2.15, respectively) provide odds ratios that are consistent with a clinically important effect. The confidence intervals that contain the treatment effect of different covariates on AER are almost identical to the effect of ACE inhibitors alone. Thus, it is not a surprise that these covariates had little effect on the beneficial outcome of ACE inhibitors.

3. How much does allowance for uncertainty change the results?

Although it is possible that the authors did not identify all relevant studies, including some smaller or unpublished studies, it is unlikely that these studies would overwhelm the consistent effect of ACE inhibitors on microalbuminuria in the subgroups studied.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. The results indicate that ACE inhibitors have a significant effect on reversing and/or preventing the worsening of albuminuria associated with type 1 diabetic renal disease. These effects occurred across a broad range of patients, regardless of age, glycemic control, gender, baseline BP or diabetes duration. The results were strongly influenced by baseline AER with the greatest reduction in AER observed in patients with the highest baseline levels. Although AER is a surrogate marker, it is a useful predictor for development and progression of nephropathy. (4) Since approximately 80% of untreated patients with type 1 DM and microalbuminuria increase their AER at a rate of 10-20% per year to the stage of overt nephropathy over a period of 10-15 years, the results of this meta-analysis will have a definite impact on patient care. (5)

2. Were all clinically important outcomes considered?

The maximum age included in the meta-analysis was 68 years; thus results would need to be extrapolated for older populations. Since AER is only a surrogate marker for underlying renal dysfunction, the results could have been strengthened by correlating the effects of ACE inhibitors with other indicators of renal function, such as a measure of glomerular filtration rate.

3. Are the likely treatment benefits worth the potential harms and costs?

Yes. Since many patients require ACE inhibitors for other indications (e.g. hypertension, congestive heart failure), these patients enjoy added benefit at no additional cost. For the patients to whom this meta-analysis most directly applies (i.e. normotensive patients with microalbuminuria), the cost and minimal side effects of an ACE inhibitor would be good value for a reduction or delay in end-stage renal disease, need for dialysis and the associated reduction in quality of life.

Commentary

This meta-analysis provides justification for initiating an ACE inhibitor in any patient with type 1 DM and microalbuminuria, even if the patient is normotensive. The appearance of clinically detectable microalbuminuria usually occurs after a period of 5-10 years following the onset of type 1 DM. Since the duration of diabetes was not found to be significant, the use of ACE inhibitors either early (at the onset of microalbuminuria) or later on in the disease process would be beneficial. The meta-analysis did show, however, that patients with greater baseline microalbuminuria have a larger proportional benefit than those with less. As well, since treatment effect was only slightly attenuated when BP reduction was taken into account, this analysis supports the results of previous studies that have also suggested that ACE-inhibitors can provide benefit independent of BP reduction. (6,7)

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Type 1 Diabetes Mellitus and Microalbuminuria: Should All Patients Receive ACE inhibitors?

Reviewer: Jodie Wong, Karen Shalansky

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Reviewer's profession/specialty: U.B.C. Pharm.D. student (JW), Dialysis Pharmacist/Residency Coordinator (KS)

Original Citation

The ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. *Ann Intern Med* 2001;134:370-379.

Overall Study Question

The effectiveness of angiotensin-converting enzyme (ACE) inhibitors in reversing and/or preventing progression of microalbuminuria in patients with type 1 diabetes mellitus (DM) is already well-established. (1,2,3) Using the rate of change of albumin excretion rate (AER) as the primary outcome measure, the main objective of this meta-analysis was to determine if there was a subgroup of patients with type 1 DM and microalbuminuria who were most likely to benefit from ACE inhibitor therapy. The subgroups identified included age, duration of diabetes, gender and glycemic control (hemoglobin A1c). The investigators also examined the impact of blood pressure (BP) and baseline AER as covariates on treatment effect. Finally, the risk for progression to macroalbuminuria and regression to normoalbuminuria was also examined.

Are the Results of the Study Valid?

1. Did the overview address a focused clinical question?

The authors could have been more explicit in phrasing their clinical questions, and could have expressed their objectives in a more concise form. They did not

delineate a priori all covariates to be considered in their objectives.

2. Were the criteria used to select articles for inclusion appropriate?

Yes. Criteria for study selection included trials with at least 10 patients who had: 1) type 1 DM; 2) normotension, as defined by each individual trial; and 3) microalbuminuria, as defined as an AER of 20-200 mcg/min measured at baseline and one or more follow-up visits. All trials were required to have a placebo or non-intervention group, and a minimum follow up of 1 year. Of note, one-third of the patients who were classified as normotensive in earlier studies were actually considered hypertensive by current standards. This variance, however, allowed the authors to observe the efficacy of ACE inhibitors over a wider range of blood pressures. Other antihypertensive medication that patients may have been taking other than ACE inhibitors were never mentioned by the authors.

3. Is it unlikely that important, relevant studies were missed?

Probably. Only one database (Medline) was employed, thus studies not indexed in this database may have been missed. However, bibliographies of published studies were also reviewed by the authors, and experts in the field were also consulted. Manufacturers or trial registries did not appear to have been contacted by the authors, and no information was provided to suggest that abstracts from

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conference proceedings were reviewed. The authors also did not specify any restrictions on their searching (i.e. years considered or languages of publication).

4. Was the validity of the included studies appraised?

No. Information was not provided on how many reviewers were involved in retrieving the studies or assessing these studies for inclusion or exclusion from the meta-analysis. The reviewers did not comment on whether or not they were blind to study results when studies were selected for inclusion.

5. Were assessments of studies reproducible?

This meta-analysis assessed raw data obtained from all trials and pooled them to create one large database. Trial investigators were contacted to obtain individual patient data with respect to the objectives of this study. This method was employed as the authors claimed that individual studies were underpowered to analyze for subgroup effects or risk for progression to macroalbuminuria. As well, analysis of individual patient data allowed a consistent approach to assess renal outcome (ie. AER), covariates, and subgroup effects.

Both a trial-level and a patient-level analysis was performed. For the trial-level analysis, both fixed-effects and random-effects models were used to provide an estimate of the treatment effect, and estimates of between-trial variance were calculated. Treatment effect was expressed as a percentage difference of the relative change in AER between treatment and control groups compared to baseline. For the patient-level analysis, a random-effects regression model was used to determine the treatment effect for each patient. The authors do not state whether certain baseline risk factors (e.g. age, diabetes duration) were analyzed as continuous or categorical variables to determine a possible interaction.

Progression to macroalbuminuria or regression to normoalbuminuria may not have been as reproducible. Macroalbuminuria and normoalbuminuria were defined as AER greater than 200mcg/min or less than 20mcg/min, respectively, on two successive occasions at least 3 months apart, or at final visit. Since some patients may have met the criteria upon their final visit, the durability of the result over time could not be assessed.

6. Were the results similar from study to study?

All trials with at least a 2-year follow-up (n=10) showed a beneficial effect of ACE-inhibitors on rate of change in AER.

What were the Results?

1. What are the overall results of the review?

Initially, 12 trials and 698 patients were included in the meta-analysis. However, final analysis of treatment effects was limited to those studies with at least 2 years of follow-up, effectively excluding 2 trials and resulting in a total of 646 patients.

ACE inhibitors used in the trials were captopril (3 trials), lisinopril (3 trials), ramipril (2 trials), enalapril (1 trial) and perindopril (1 trial). Overall, at two years and using a random-effects model, AER was 50.2% (95% CI, 30.0%-64.6%, $p<0.001$) lower in patients receiving ACE inhibitors as compared to placebo. When the impact of a reduction in blood pressure on AER was accounted for, the treatment effect was attenuated slightly to 45.1% ($p<0.001$). A more pronounced reduction in AER was noted among subjects who had a baseline AER at the upper end of microalbuminuria (200 mcg/min) compared to those at the lower end (20 mcg/min) (74.1% vs. 17.8%, respectively, $p=0.04$). Other covariates (age, diabetes duration, sex, glycemic control) had no apparent impact on treatment effect.

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Progression to macroalbuminuria decreased by one-third as compared to placebo, with an odds ratio (OR) of 0.38 (95% CI, 0.25-0.57, $p < 0.001$) in favour of the ACE inhibitor. As well, there was a threefold increase in regression to normoalbuminuria with an OR of 3.07 (95% CI, 2.15-4.44, $p < 0.001$). All trials demonstrated beneficial effects of ACE inhibitors with respect to regression to normoalbuminuria, and all were favourable except for one regarding risk for progression to macroalbuminuria.

2. How precise were the results?

Both fixed-effects and random-effects models showed similar results on rate of change of AER. A marginal attenuation in treatment effect was observed using the estimates derived from the patient-level rather than trial-level regression models. The confidence intervals around the treatment estimate for the progression to macroalbuminuria and the regression to normoalbuminuria were fairly narrow. The lower boundary of both confidence intervals (0.25 and 2.15, respectively) provide odds ratios that are consistent with a clinically important effect. The confidence intervals that contain the treatment effect of different covariates on AER are almost identical to the effect of ACE inhibitors alone. Thus, it is not a surprise that these covariates had little effect on the beneficial outcome of ACE inhibitors.

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2. Were all clinically important outcomes considered?

The maximum age included in the meta-analysis was 68 years; thus results would need to be extrapolated for older populations. Since AER is only a surrogate marker for underlying renal dysfunction, the results could have been strengthened by correlating the effects of ACE inhibitors with other indicators of renal function, such as a measure of glomerular filtration rate.

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side effects of an ACE inhibitor would be good value for a reduction or delay in end-stage renal disease, need for dialysis and the associated reduction in quality of life.

Commentary

This meta-analysis provides justification for initiating an ACE inhibitor in any patient with type 1 DM and microalbuminuria, even if the patient is normotensive. The appearance of clinically detectable microalbuminuria usually occurs after a period of 5-10 years following the onset of type 1 DM. Since the duration of diabetes was not found to be significant, the use of ACE inhibitors either early (at the onset of microalbuminuria) or later on in the disease process would be beneficial. The meta-analysis did show, however, that patients with greater baseline microalbuminuria have a larger proportional benefit than those with less. As well, since treatment effect was only slightly attenuated when BP reduction was taken into account, this analysis supports the results of previous studies that have also suggested that ACE-inhibitors can provide benefit independent of BP reduction. (6,7)

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1. EUCLID Study Group. Randomized placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. *Lancet* 1997;349:1787-92.
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Issues in Pharmacotherapy Practice

Articles in this section are designed to provide today's pharmacotherapy practitioners with perspective on a wide range of drug-related issues and provide insight on improving the rationale use of drugs.

Pharmacotherapy Reviews

State-of-the art systematic reviews of topical pharmacotherapy issues. The principles of evidenced-based medicine are required for submission of all pharmacotherapy review articles with a focus on clinically relevant issues in pharmacotherapy practice to ensure readers can apply these findings to daily practice.

Pharmacotherapy Updates

Pharmacotherapy updates are not designed to be comprehensive systematic reviews but should be brief, focused reports on recent advances in pharmacotherapy. Summary of consensus conference and position statements pertinent to pharmacotherapy can also be included.

Formulary Reviews

Reviews on new drugs or drug classes with comprehensive description of pharmacology, pharmacokinetics, indication, drug interactions, efficacy, toxicity and cost. Relation of new drugs to others in the same class and conclusions about the role of new agents are required when applicable.

Drug Information

Drug information submissions are designed to provide brief response to specific therapeutic questions or controversies. This section is ideally presented in a question-and-answer format.

Innovative Practice

Reports on innovative pharmacotherapy practices highlighting advanced practitioner roles and their impact on patient outcomes. Reports on the use of information technology and/or informatics in advancing clinical practice and research are encouraged.

Commentaries

Commentaries are designed to provide opinion on pertinent issues in pharmacotherapy practice. Perspective on selected areas of drug therapy and personal experiences are encouraged for all submissions in this section. Commentaries directed toward a specific specialty are also encouraged.

For further information on submitting a manuscript to the Issues in Pharmacotherapy Practice section of The Journal of Informed Pharmacotherapy please see the [For Authors](#) section of our website. All manuscripts must be submitted by e-mail as an attachment to [The Editor](#) at the Journal of Informed Pharmacotherapy.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;8:400.

An Assessment of Quality of Sleep and the Use of Drugs with Sedating Properties in Hospitalized Adult Patients

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 2001.

Context

Insomnia is a common subjective complaint that occurs in up to 25% of the general population and frequently occurs in the acute hospital setting. While benzodiazepines are commonly used to treat insomnia, adverse effects with chronic benzodiazepine use are resulting in patients seeking alternatives such as natural or herbal medications.

Objectives

To assess sleep disturbance and to characterize factors influencing sleep including the use of drugs with sedating properties.

Setting

A major Canadian tertiary adult acute care teaching hospital.

Design

This single-centre prospective study involved patients admitted to the General Medicine and Family Practice wards during a 70-day period.

Main Outcome Measures

Consenting patients were requested to provide information regarding pre-admission drug use and sleep patterns. Sleep was assessed using validated 100mm visual analogue Verran and Snyder-Halpern (VSH) sleep scales. Questionnaires were completed by patients on a daily basis to characterize 3 sleep dimensions: sleep disturbance, effectiveness and supplementation. Patients were also asked to identify factors influencing sleep while in hospital. The VSH sleep scale scores in each dimension were then compared to population statistics. The use of drugs with sedating properties prior to and during hospitalization was also assessed.

Results

During the 70-day study period, 100 patients completed 339 study questionnaires. A review of the provincial community prescription database (PharmaNet) revealed that 35% of patients were prescribed a hypnotic or antidepressant drug that was administered at bedtime in the 3-month period prior to admission. During hospitalization, 60% of enrolled patients were prescribed zopiclone or a benzodiazepine for bedtime hypnotic use. Overall, 44% of total patient observations revealed some type of sleep disturbance of which pain was the most common factor, followed by needing to go to the bathroom, shortness of breath (SOB), or a combination of these three factors. The mean total sleep disturbance score was 306 (maximum possible score 700; range 13 - 700). The mean total sleep effectiveness score was 301 (maximum possible score 500; range 61 - 500). The mean total sleep supplementation score was 76 (maximum possible 400; range 0 - 372). Twenty-nine percent of patients had a hypnotic prescription initiated in hospital, while there was no evidence of pre-admission hypnotic use.

Conclusions

Sleep quality in hospitalized adult patients at Vancouver General Hospital (VGH) was similar to that reported for institutionalized patients in the US and poorer than reported for non-institutionalized patients. The results of this study reveals that insomnia continues to be a problem that affects hospitalized adult medical service patients and a relatively high percentage of these patients are being prescribed a hypnotic prior to and during hospitalization.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;8:401.

Pharmacist Utilization of the DIE Test to Assess Aminoglycoside Vestibulotoxicity

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 2001.

Context

Aminoglycoside antibiotics can cause irreversible vestibulotoxicity, which has debilitating effects on balance and vision. The dynamic illegible E (DIE) test was developed to screen for signs of vestibulotoxicity and prevent permanent vestibular damage and is currently being conducted by the neurophysiologist.

Objectives

The primary goal of this study was to show that a pharmacist can perform the DIE test for vestibulotoxicity with equivalent accuracy to the neurophysiologist. The secondary goals were to determine the workload of conducting the DIE test and to correlate patient variables to vestibular toxicity.

Setting

A tertiary Care 1000-bed university-affiliated Hospital.

Design

All patients initiated on aminoglycoside therapy were screened over a 12-week period. All patients greater than 18 years of age and prescribed aminoglycoside therapy for more than 7 days were evaluated for DIE test administration. Patients were excluded if they were unable to sit up to perform the test, unable to read at least the top four rows of the test chart due to visual impairment or mental incompetence, had a language barrier without a translator available or had a medical contraindication

to neck manipulation. Eligible patients were tested first by the primary investigator then retested by the neurophysiologist within 72 hours.

Main Outcome Measures

The primary goal was to show that a pharmacist can perform the DIE test for vestibulotoxicity with equivalent accuracy to the neurophysiologist. The secondary goals were to determine the workload of conducting the DIE test and to correlate patient variables to vestibular toxicity.

Results

Two hundred and thirteen patients were screened with 39 receiving aminoglycosides for more than 7 days. Fifteen patients were excluded due to medical condition or discharge from hospital before testing and 24 were tested by the primary investigator. The neurophysiologist was not able to retest 7 of these patients therefore 17 patients were included in the analysis. There was a 100% correlation between the results of the primary investigator and the neurophysiologist. There were no positive test results (score ≥ 3), therefore no patients with vestibulotoxicity. No aminoglycoside doses were supratherapeutic and there were no changes in baseline patient variables such as serum creatinine or blood urea nitrogen. The DIE test took less than 3 minutes to administer. On average, only 2-3 patients per week would require this test resulting in a minimal increase in pharmacist workload.

Conclusions

A pharmacist can perform the DIE test with equivalent accuracy to the control tester and incorporate this monitoring technique into the scope of their daily activities.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;8:402.

Assessment of Outcomes of Intradialytic Parenteral Nutrition

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 2001. (2001 BC CSHP Research Project Award Winner)

Context

Patients with end-stage renal disease often suffer from malnutrition. One modality used to treat malnourished hemodialysis patients is intradialytic parenteral nutrition (IDPN), a multi-component nutritional supplement.

Objectives

The primary outcome of this trial was to determine the effects of IDPN on weight and serum albumin in a large tertiary-care institution.

Setting

A 160 bed hospital-based hemodialysis unit.

Design

All patients who received IDPN for greater than 1 month from program inception in June 1997 to December 2000 were analyzed. Patients received IDPN as amino acid 10% 250mL or 500mL, dextrose 50% 250mL and fat emulsion 20% 250mL. IDPN was administered during each hemodialysis run three times weekly. Data was collected at 6 and 3 months prior to IDPN administration as well as at baseline, 3, 6, 9, and 12 months post-therapy.

Main Outcome Measures

Therapeutic efficacy was assessed by percent change from baseline of dry weight and serum albumin.

Results

Twenty-six courses of IDPN in 24 patients met inclusion criteria. The mean duration of treatment was 4.3 months. A significant decline in dry weight was observed at both 6 and 3 months prior to IDPN initiation. Dry weight increased from baseline and achieved significance at 6, 9 and 12 months post-therapy. Serum albumin also significantly improved from baseline at 3 and 9 months. Compared to baseline, there was a 3 to 5-fold increase in the percent of patients with serum albumin greater than or equal to 34g/L. Adverse drug reactions consisted primarily of excess fluid gain and hyperglycemia.

Conclusions

IDPN significantly increased both weight and serum albumin in malnourished hemodialysis patients.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;8:403.

Characterizing and Developing Strategies for the Treatment of Community-acquired Pneumonia at a Community Hospital

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 2001. (This project was conducted through the B.C. Hospital Pharmacy Residency Program under no financial support or external affiliations)

Context

Patients admitted to Lions Gate Hospital with a primary diagnosis of community-acquired pneumonia (CAP) have a mean length of stay (LOS) of 9.1 days compared to 7.9 days for peer group hospitals. This difference of 1.2 days results in an annual potential bed day savings of 397 and warranted an investigation into the management of CAP.

Objectives

To characterize and provide recommendations for the management of CAP at our institution.

Setting

A Canadian community hospital consisting of 260 acute and 325 extended care beds.

Design

A retrospective chart review was conducted for patients admitted with a primary diagnosis of CAP between May 1, 2000 and August 31, 2000.

Main Outcome Measures

Data collected included: 1) the decision to hospitalize based on the calculated PSI score, 2) whether

guideline-recommended diagnostic tests (chest X-ray, sputum and blood cultures) were performed, 3) antibiotic selection for pneumonia in terms of choice, route and cost, 4) timing and appropriateness of step-down (SD) from IV to PO antibiotics, 5) whether early discharge occurred and 6) length of stay.

Results

Fifty-one patients were included in the study with an average age of 75 ± 15 years. These patients had a mean LOS of 9.9 days, and a median LOS of 5 days. Based on Pneumonia Severity Index (PSI) scores calculated for each patient, eight patients could have potentially been treated on an outpatient basis with a low risk of mortality from CAP. Initial empiric antibiotic choices were consistent with the Canadian CAP guidelines in 53% of patients, with inconsistencies arising mainly due to cephalosporin monotherapy and azithromycin monotherapy regimens being prescribed. Step-down (SD) from IV to PO antibiotics occurred in approximately 39% of patients. An additional 24% of patients could have been stepped-down, and SD was not applicable in 37% of patients. The potential annual cost avoidance from implementing admission criteria based on a PSI score, applying SD criteria and promoting early discharge criteria was estimated to be \$206,300.

Conclusions

Considerable variability exists in the treatment and management of CAP. A CAP pre-printed order sheet was developed in order to address the issues identified in this study and provide consistency in the management of CAP at our institution.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;8:404.

Role of Cytomegalovirus (CMV) Antigenemia Assay for Detection and Prevention of CMV Syndrome/disease in Solid Organ Transplant (SOT) Recipients

ED Greanya, BSc (Pharm), N Partovi, PharmD FCSHP, M Conci, BSc (Pharm), RJ Shaprio, MD FRCP, E Yoshida, MD FRCP, R D Levy, MD FRCP, CH Sherlock, MD FRCP, GM Stephens, MD FRCP

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 2001.

Context

The CMV antigenemia assay has been used in recent years as a means of guiding the preemptive therapy of CMV disease in SOT. More recently, concerns have been raised regarding the utility of the test to accurately and precisely detect the virus early enough to reduce morbidity and mortality caused by CMV in transplant recipients.

Objectives

The primary objective of our study was to determine the performance characteristics of our current method of antigenemia testing in our SOT population.

Setting

A large Canadian teaching hospital.

Design

We retrospectively reviewed the charts of all SOT recipients between January 1, 1999 and June 31, 2000 for the 6 months following transplantation. Physical exam, laboratory and treatment information was collected throughout the follow-up period.

Main Outcome Measures

Sensitivity, specificity and predictive values for CMV antigenemia tests.

Results

Of 155 transplant recipients, 21 met our pre-specified exclusion criteria, leaving us with a sample size of 134 patients receiving kidney, liver, lung and kidney-pancreas transplants. The overall performance of our antigenemia assay were as follow; sensitivity 64%, specificity 81%, positive predictive value 76%, negative predictive value 71%. Performance characteristics were also assessed, taking into account baseline recipient and donor serology and test breakpoints used to determine a positive test result. A mean of 18 days passed between onset of signs and symptoms of CMV disease/syndrome and the first recorded positive test result and only 26% of patients had a positive test result before the onset of symptoms. It was found that an antigenemia test result of ≥ 1 cell resulted in the most sensitive and specific results, with an increased odds ratio of developing CMV disease.

Conclusions

Our current method of antigenemia testing to guide preemptive ganciclovir therapy in SOT patients is not optimal in terms of performance characteristics or for detecting disease early. More study is needed on new molecular testing to determine if our ability to predict CMV disease can be improved.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;8:405.

A Comparison of Two Dosage Regimens of Intravenous Vancomycin in Hemodialysis Patients

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Pharmacy Department, St. Paul's Hospital, Vancouver, British Columbia, Canada

Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 2001.

Context

High-flux hemodialysis removes significant amounts of vancomycin. There is currently no consensus on the optimum dosing regimen for vancomycin for patients receiving intermittent high-flux hemodialysis.

Objectives

Our objective was to compare the pharmacokinetic and clinical outcomes achieved by two commonly used intravenous vancomycin dosing regimens in this population.

Setting

A 43 bed hemodialysis unit in a urban, teaching hospital.

Design

We performed a prospective, randomized, unblinded study, in which patients, after receiving vancomycin 25mg/kg as a loading dose, were randomized to receive either vancomycin 500mg every dialysis (Q Dialysis regimen) or 20mg/kg every 2nd dialysis (Q 2nd Dialysis Regimen) as a maintenance regimen. All doses were administered during the last 1-2 hours of dialysis.

Main Outcome Measures

We compared the proportion of therapeutic trough serum vancomycin concentrations achieved by both maintenance regimens using a predefined therapeutic range of 10-20mg/L.

Results

Fifteen patients were included in our study (8 with Q Dialysis dosing and 7 with Q 2nd Dialysis dosing). At steady state, 5/7 serum levels in the Q Dialysis group were therapeutic, with one subtherapeutic level, one supratherapeutic level, and one level not drawn. Four of five levels in the Q 2nd Dialysis group were therapeutic with one subtherapeutic level and two levels not drawn. Five patients required changes in their treatment regimens (two in the Q Dialysis group, three in the Q 2nd Dialysis group). No patients were withdrawn from either study regimen due to treatment failure, defined by a change to a different antimicrobial agent because of worsening condition or death during treatment.

Conclusions

Both study regimens appear to achieve similar pharmacokinetic as well as clinical outcomes; however, further patient enrollment and data collection are necessary before any definitive conclusions can be made. Based on subjective feedback from pharmacy and nursing staff, and fewer protocol violations, the Q Dialysis regimen appears to be more practical and convenient to implement.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;8:406.

Comprehensive Assessment of Angiotensin Converting Enzyme Inhibitor Compliance in Patients with Heart Failure

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 2001.

Context

While intervention by pharmacists can improve patients' adherence with medication regimens, limited resources prevent one-on-one counseling with all patients. Identifying patient characteristics associated with non-compliance could help pharmacists target patients most likely to benefit from programs aimed at optimizing adherence.

Objectives

To identify patient variables associated with non-compliance of angiotensin converting enzyme (ACE) inhibitor in heart failure (HF) patients in an effort to target patients most likely to benefit from intervention.

Setting

All patients were admitted to a 400 bed teaching institution; however, data reflects the period of time prior to hospital admission.

Design

Patients admitted to St. Paul's Hospital coronary care unit (CCU), general cardiology ward, and general medicine ward who had been taking an ACE inhibitor for at least 3 months prior to admission were approached for consent to participate in this study. An interview was carried out using a standardized survey. The survey consisted of questions relating to patient's demographics, medication use, perceived need of ACE inhibitor therapy, traveling, deliberate alteration from prescribed regimen, use of

compliance aids, rating of physician and pharmacist, cost issues and drug information sources. PharmaNet records, patient-specific prescription medication records for the past fourteen months, were obtained for compliance calculation.

Main Outcome Measures

The primary outcome was the rate of compliance to a prescribed ACE inhibitor regimen as determined by PharmaNet records. Univariate analysis was used to identify patient variables that might be individually associated with non-compliance. Multivariate logistic regression was then used to identify independent predictors of non-compliance.

Results

Eighty-eight out of ninety-nine patients were included in the study. The response to two questions were identified as independent predictors of non-compliance: "Are you careless at times about taking your medicine?" and "Have you discontinued taking any of your medications that your physician intended you to take in the past year?". The sensitivity was 40% and the specificity was 96%. Variables which have been reported to predict non-compliance in previous studies, were not found to be independent predictors in our study.

Conclusions

The answers to two questions help target specific HF patients for interventions aimed at improving compliance. However, the results drawn are based on a relatively small sample and could be affected significantly by small changes in the pattern of respondents.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;8:407.

The Effect of Chronic Dosing of Probenecid on Cefazolin Serum Concentrations

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 2001.

Context

Probenecid can increase the serum concentrations of drugs that are eliminated principally by renal secretion such as cefazolin. The use of probenecid concurrently with cefazolin could result in elevated cefazolin levels above the minimum inhibitory concentration (MIC) and longer dosage intervals.

Objectives

Compare the serum levels produced by dosing cefazolin 2000mg IV Q8H to the levels produced by dosing cefazolin 2000mg IV OD plus probenecid 500mg PO QID.

Setting

Inpatients with infections requiring cefazolin treatment in a Community-based Teaching Hospital and outpatients presenting to the Emergency Department of the same hospital for the treatment of cellulitis.

Design

Patients in this prospective, non-randomized, unblinded study, were identified after an order was written for cefazolin 2000mg IV Q8H or 2000mg IV daily plus probenecid 500mg PO QID. For both study arms, a peak cefazolin level was drawn an hour after the infusion was started. Likewise, a cefazolin level was drawn 23 hours later prior to that next scheduled dose. Doses of cefazolin for days 2 through 4 were then administered as ordered. On day 5, peak and trough levels were drawn an hour after the infusion started and 23 hours later respectively.

Main Outcome Measures

Peak and trough cefazolin serum levels on days one and five. Treatment success. Treatment side effects.

Results

A total of 19 patients were prospectively assessed from April 2000 to February 2001. Sample # Daily cefazolin (n=14)(mg/L) Q8H cefazolin (n=5)(mg/L) Day #1 peakday #1 troughday #5 peakday #5 trough 151.50 +/- 41.832.00 +/- 1.86160.38 +/- 26.961.95 +/- 1.73 122.15 +/- 45.3118.65 +/- 13.90136.51 +/- 52.5216.98 +/- 6.67 There were 12 (86%) treatment successes in the once daily arm and 4 (80%) treatment successes in the three times daily arm.

Conclusions

Probenecid 500mg PO QID was effective in maintaining cefazolin serum levels above the MIC90 for Staphylococcus aureus for the duration of the 24 hour dosing interval. First dose effects of probenecid were not enhanced by repeated doses of probenecid and finally, once daily cefazolin plus probenecid was an effective treatment for cellulitis through an outpatient parenteral antibiotic therapy (OPAT) setting, producing acceptable side effects.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;8:408.

Physician and Pharmacist Managed Warfarin Treatment in Open Heart Surgery Patients

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 2001.

Context

Surgeons have historically adjusted the dosage of warfarin in our institution. To more efficiently utilize the skills of both surgeons and pharmacists, the dosage of warfarin was delegated to pharmacists.

Objectives

To compare the effectiveness of pharmacists to physicians in obtaining therapeutic anticoagulation upon initiation of warfarin therapy. Secondary objectives included: the percentage of days when the INR was >4 or <2 , the time to stabilize the INR within the therapeutic range, and the percentage of patients experiencing at least one major bleed.

Setting

Cardiac Surgery wards of a tertiary teaching hospital.

Design

This study was a retrospective chart review of patients who received warfarin following cardiac valve surgery. Pharmacists utilized a warfarin nomogram to manage patients; physicians dosed independently.

Main Outcome Measures

Percentage of therapy days within the target INR range; percentage of therapy days with INR less than 2 or greater than 4.

Results

This study consisted of 227 patients (pharmacist group: 97; physician group: 130). There was no difference found between the two groups in the percentage of days in the therapeutic range (p-value=0.27), the percentage of days with INR <2 (p-value=0.06), the percentage of patients discharged before their INR stabilized (p-value=0.91) and the percentage of patients with a major bleed (p-value=0.72). The pharmacist group had 6% fewer days of INR >4 than the physician group and this was statistically significant (p-value of <0.001).

Conclusions

Pharmacists are equally safe and effective as physicians when managing warfarin therapy in patients who have undergone cardiac valve replacement.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;8:409.

Risk Factors for the Development of Thrombocytopenia in the ICU: a Validation Model

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 2001.

Context

Thrombocytopenia is common in critically ill patients and is associated with increased duration of hospital stay and higher mortality. While a moderate decline in platelet count does not present a serious risk to most patients, clinicians often intervene in an attempt to prevent life-threatening outcomes associated with severe thrombocytopenia, or thrombosis associated with heparin-induced thrombocytopenia (HIT). A wide range of potential causes of thrombocytopenia have been reported in the literature, but study results have been inconsistent making treatment decisions difficult.

Objectives

To identify independent risk markers for thrombocytopenia in ICU patients at a teaching hospital. A secondary objective was to compare these risk markers to those identified in a previous study carried out at a community hospital ICU.

Setting

Fifteen bed Intensive Care Unit (ICU) in a teaching hospital.

Design

Retrospective study involving 276 consecutive patients meeting inclusion criteria.

Main Outcome Measures

Univariate and multivariate logistic regression analyses were used to identify independent risk markers present on admission and throughout the ICU stay.

Results

Thrombocytopenia developed in 54 (19.6%) patients. Independent risk markers included mechanical ventilation (odds ratio [OR], 11.1; 95% confidence interval [CI], 1.4-88.2; $p=0.023$), dobutamine (OR, 4.9; 95% CI, 2.2-11.2; $p<0.001$), packed red blood cell transfusions (OR, 2.5; 95% CI, 1.2-5.2; $p=0.010$), dopamine (OR, 2.0; 95% CI, 1.04-4.0; $p=0.053$) and APACHE II score (OR per 5 unit increase, 1.4; 95% CI, 1.1-1.7; $p<0.001$). Two variables were associated with a lower risk of thrombocytopenia: admission platelet count (OR per $50 \times 10^9/L$ increase, 0.6; 95% CI, 0.5-0.8; $p<0.001$) and cefuroxime (OR, 0.4; 95% CI, 0.2-1.2; $p=0.101$). Three variables were common to both the teaching and community hospital models: admission platelet count, APACHE II score and the transfusion of packed red blood cells. Heparin was not identified as a risk marker in either the teaching or community hospital population. In both populations, thrombocytopenia was associated with a greater mortality rate and longer hospital and ICU stays.

Conclusions

Risk markers for the development of thrombocytopenia in ICU patients at an academic hospital include mechanical ventilation, transfusions, admission platelet count, medications and APACHE II score. There is substantial overlap with risk markers identified at a community hospital setting.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;8:410.

Evaluation of Quality of Life in Patients with Congestive Heart Failure Attending a Community Hospital's Heart Function Clinic

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 2001.

Context

A multidisciplinary heart function clinic (HFC) was opened to better facilitate outpatient follow-up for people with congestive heart failure (CHF). Two goals of the HFC were to improve patients' quality of life (QOL) and to bring patients' medication therapy in line with the 1999 American guidelines for CHF management. To date, no published studies have evaluated QOL in patients on these medications while attending a multidisciplinary outpatient HFC.

Objectives

To determine the impact of a multidisciplinary HFC on QOL, medication therapy, and medication compliance in patients with CHF.

Setting

A Canadian community hospital consisting of 260 acute and 325 extended care beds.

Design

This was a prospective, observational study.

Main Outcome Measures

To assess QOL, the Short Form 36 (SF-36) Health Status Survey, the Minnesota Living With Heart Failure (MLWHF) Questionnaire, and a global assessment of health were conducted at baseline and after three months, at which time drug therapy and compliance were also assessed.

Results

At follow-up, the clinic group's MLWHF total score was three times better, their physical score was 3.5 times better, and their emotional score was two times better than the control group's scores, respectively. Clinic patients were more likely than control patients to receive beta-blockers and spironolactone when these drugs were indicated. Clinic patients reported higher compliance than control patients.

Conclusions

QOL and medication therapy showed a greater improvement in the clinic group than the control group.

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Technology in Practice Section (TIPS)

(formerly "Pharmacotherapy on the Web")

[The JIP Website Review / Rating System](#) | [Online Site Submission Form](#) | [Other Suggestions/Comments](#)

"Our Age of Anxiety is, in great part, the result of trying to do today's jobs with yesterday's tools." These words of the distinguished communications theorist Marshall McLuhan were never more true. Today's health practitioners are constantly challenged by the increasing volume of health information, the changing technology skills required, and avoiding both information overload and anxiety. Pharmacotherapy practitioners require a core level of technology competence in order to keep pace with patient needs in today's health systems. A lack of technology skills might lead to anxiety, information overload and suboptimal patient care.

We agree with a January 2001 editorial which states that pharmacists have not been at the forefront of integrating available technologies into their practice settings and that there is a "worrisome" technology gap in our profession.⁽¹⁾ A survey we conducted at our institution in May 2001 indicated that the greatest work-related technology challenge that pharmacists perceived was a lack of skills required to effectively use currently available technology and on-line resources for patient care. The vast majority of the respondents believed that their practice effectiveness would significantly increase if their computer, Internet, and information management skills could be improved.

The purpose of the TIPS is to empower readers with the knowledge required to integrate technology into their practice to improve patient care, research, education and life-long learning effectiveness. The section of the JIP will focus on technologies that are currently available, ubiquitous and can be procured "off-the-shelf" by individuals. The TIPS will expand the scope of the "Pharmacotherapy on the Web" section, which has been part of the JIP since its inception. Web site reviews will expand to include resources that provide content on information management and computer skills.

We invite readers to guide the subject matter of the TIPS section by **submitting questions and topic suggestions**. We are interested in hearing about what your technology related challenges are and hope to provide a forum for addressing some of the questions you have. Also, we invite you to submit a description of the innovative solutions that you have developed to meet some of these challenges in your practice setting.

The TIPS section of the JIP will feature topics such as:

- How to use the Internet to help you keep up with the literature and improve your

practice

- How to choose and use a personal digital assistant (PDA) for you practice
- Critical evaluations of drug and disease information software
- How to manage and organize your professional resource material
- How to make your pertinent resources electronically available to you in your practice area
- Methods for optimizing internet and medical database search strategies
- Regaining control of your email in-box
- Forums for reader-initiated information exchange
- Knowledge management and knowledge sharing in practice

We look forward to your questions and hearing about your day-to-day technology-related challenges.

Are you a health care professional and know of a useful site for your practice? Submit it to us for review.

The Journal of Informed Pharmacotherapy Website Review / Rating System

The purpose of JIP Web reviews is to answer the following question about the site:

How USEFUL is it to pharmacotherapy practitioners? (i.e., is it likely to assist clinicians or researchers in making clinical decisions or advancing their skills?)

This is answered by evaluating sites according to the following criteria:

1. Is the information **COMPLETE** (i.e., in-depth) enough to meet it's claimed or perceived objectives? (/5)

2. Is the information **CREDIBLE** (i.e., accurate, unbiased)? (/5)

a. Is it written/compiled by health care professionals?

- i. Are they pharmacotherapy specialists? (i.e., pharmacists, physicians)
- ii. If not, it is clear what the credentials of the people are?

- are they acceptable? (i.e., other health care professional? Medical journalists? laypeople?)

- iii. Does the site facilitate contacting the authors of the information if desired?

b. Is the SOURCE(s) of the information clear and reliable?

- i. Peer-reviewed research (BEST)
- ii. Non-peer-reviewed research
- iii. Reports/summaries of above research
- iv. Tertiary information databases (e.g.. online textbooks, drug databases, guides to other sites)
- v. Expert opinion
- vi. Lay-press
- vii. Drug company press releases
- viii. Non-expert opinion (WORST)

- If the information is not generated by the maintainers of the site, does it provide direct HTML linkage to the original source of the information?

c. Is the information UP-TO-DATE?

- i. Is it clear when all pages were last updated?
- ii. Is the frequency of updates appropriate for the type of information?

d. Are the sponsors of the site clearly indicated?

- i. If so, is it possible that the information may be biased?

- 1.evidence-based medicine organizations (BEST)
- 2.“independent” sites
- 3.clinical societies/associations
- 4.industry-sponsored
- 5.industry-maintained (WORST)

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3. Is the site well-designed (**USABILITY**)? (/5)

- a. Is it esthetically pleasing?
- b. Does it employ generally accepted principles of good web design?

- i. Intuitive navigation structure
- ii. Bandwidth requirements appropriate for most intended users of the site
- iii. Clear links to webmaster/site designers for feedback

- c. Does it employ advanced technologies appropriately to better fulfill its purpose? (eg. javascripts, streaming media, active server pages, DHTML)

i. If so, are they easy to use and fully functional?

4. Does the site have a particularly innovative purpose or feature that compensates for any shortcomings identified above?

SAMPLE OF THE J.I.P. WEBSITE REVIEW FORMAT:

Name of site:	
Type of site:	
Authoring organization:	
Sponsors:	
Of particular interest to:	
COMPLETENESS SCORE (/5)	
CREDIBILITY SCORE (/5)	
USABILITY SCORE (/5)	
Why it useful? (what will it help me DO?):	
Commentary:	
URL of site:	
Reviewed by:	

For links to [sites previously reviewed](#) in this section, plus many more EBM links, go to the [LINKS](#) page.

Please direct any inquiries or comments about the Journal to the Publishing Editors. If you have any recommendations for journal content, we would be pleased to receive your ideas.

Last updated: April 19, 2002

The Journal of Informed Pharmacotherapy



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Pharmacotherapy on the Web

Online Site Submission Form

We welcome submissions for this section from health care professionals. We cannot guarantee that we will publish your review in the Journal. We require full and accurate contact information for all submitters so we may clarify any aspects of your review if necessary. Your name and/or e-mail address may be included in the final publication of your review.

The purpose of JIP Web reviews is to answer the following question about the site: **How USEFUL is it to pharmacotherapy practitioners? (i.e., is it likely to assist clinicians or researchers in making clinical decisions or advancing their skills?)**

Please complete the form and scoring system below to rate the site:

[FrontPage Save Results Component]

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NAME OF SITE:

URL OF SITE:

TYPE OF SITE:

AUTHORING ORGANIZATION:

SPONSOR(S) OF THE SITE:**OF PARTICULAR INTEREST TO:**

Is the information **COMPLETE** (i.e., in-depth) enough to meet it's claimed or perceived objectives?

SCORE:

Is the information **CREDIBLE** (i.e., accurate, unbiased)? [HELP WITH SCORING](#)

SCORE:

Is the site well-designed? (**USABILITY**) [HELP WITH SCORING](#)

SCORE:

4. Does the site have a particularly innovative purpose or feature that compensates for any shortcomings identified above?

Describe:

WHY IS IT USEFUL? (WHAT WILL IT HELP USERS DO?)**COMMENTS:**

When you press "Submit to Editors", a verification page will appear confirming your submission. Please print that page for later referral.

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JIP Help: Scoring for Pharmacotherapy on the Web Section

Is the information **CREDIBLE** (i.e., accurate, unbiased)?

Questions to ask yourself in evaluating this parameter:

a. Is it written/compiled by health care professionals?

- i. Are they pharmacotherapy specialists? (i.e., pharmacists, physicians)
- ii. If not, it is clear what the credentials of the people are?
 - are they acceptable? (i.e., other health care professional? Medical journalists? laypeople?)
- iii. Does the site facilitate contacting the authors of the information if desired?

b. Is the SOURCE(s) of the information clear and reliable?

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- ii. Non-peer-reviewed research
- iii. Reports/summaries of above research
- iv. Tertiary information databases (e.g.. online textbooks, drug databases, guides to other sites)
- v. Expert opinion
- vi. Lay-press
- vii. Drug company press releases
- viii. Non-expert opinion (WORST)
- If the information is not generated by the maintainers of the site, does it provide direct HTML linkage to the original source of the information?

c. Is the information UP-TO-DATE?

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d. Are the sponsors of the site clearly indicated?

- i. If so, is it possible that the information may be biased?
 - 1.evidence-based medicine organizations (BEST)
 - 2.“independent” sites

- 3.clinical societies/associations
- 4.industry-sponsored
- 5.industry-maintained (WORST)

ii. If advertising is used on the site, can it be clearly distinguished from the other content on the site?

JIP Help: Scoring for Pharmacotherapy on the Web Section

Is the site well-designed? (USABILITY)

Questions to ask yourself in evaluating this parameter:

- a. Is it esthetically pleasing?
- b. Does it employ generally accepted principles of good web design?
 - i. Intuitive navigation structure
 - ii. Bandwidth requirements appropriate for most intended users of the site
 - iii. Clear links to webmaster/site designers for feedback
- c. Does it employ advanced technologies appropriately to better fulfill its purpose? (eg. javascripts, streaming media, active server pages, DHTML)
 - i. If so, are they easy to use and fully functional?

Pharmacotherapy on the Web

The Journal of Informed Pharmacotherapy 2002;8:500.

HealthySkepticism.org, Health Protection Branch Drug Advisories

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[HealthySkepticism.org](#), [Health Protection Branch Drug Advisories](#),

Name of site:	HealthySkepticism.org
Type of site:	Awareness site focusing on the influence of the Pharmaceutical industry on caregivers and the public.
Authoring organization:	HealthySkepticism.org, formerly known as the Medical Lobby for Appropriate marketing (MaLAM)
Sponsors:	Subscribers, WHO's Drug Action Program, several Australia/New Zealand medical organizations, Health Action International
Of particular interest to:	Physicians, pharmacists, health policymakers, the general public.
Completeness Score (/5)	4 (several hyperlinks are dead)
Credibility Score (/5)	5
Usability Score (/5)	4
Why is it useful? (what will it help me DO?):	This site is an excellent repository of stories published in the mainstream media concerning the influence of the pharmaceutical industry on prescribing practices and drug usage by the public.
Commentary:	In addition to providing well-referenced general information to consumers and health care providers about the (negative) influences of drug marketing, promotion, and other activities of pharmaceutical companies, this site provides a quick way for interested readers to view articles from around the world from the lay-press (mainly newspapers) about this topic. The most complete information is in the "Special Reports" section. The site is up to date, with articles from January 2002 already posted for viewing. There is an excellent collection of quotations as well.
URL of site:	http://www.healthyskepticism.org
Reviewed by:	Peter Loewen, Pharm.D.

Name of site:	Health Protection Branch Drug Advisories

Type of site:	E-mail alert service
Authoring organization:	Canadian Government Health Protection Branch, Therapeutic Products Directorate (TPD)
Sponsors:	as above
Of particular interest to:	Pharmacotherapy practitioners in Canada
Completeness Score (/5)	4
Credibility Score (/5)	4.5
Usability Score (/5)	4
Why is it useful? (what will it help me DO?):	Stay up to date via e-mail with the most serious drug-related safety concerns originating with the Health Protection Branch in Canada
Commentary:	This site, which could be considered the Canadian counterpart to the FDA's MEDWATCH e-mail alert service, provides subscribers (free) with periodic advisories via e-mail on safety issues in Canada. Only around 1 advisory per month is sent, so there seems to be little risk of e-mail overload by subscribing. Of course, only the most serious drug-related issues make it to this level, so this is not a "digest" of adverse reactions. Rather, it is essential reading for any drug therapy practitioner, since it is hardly acceptable to not even be aware of the advisories issued by the HPB. Unfortunately, the e-mail message sent contains little useful information about the actual advisory which prompted it. Instead, a link is provided which takes you to the HPB website where the latest advisories are listed.
URL of site:	http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/advhp_e.html
Reviewed by:	Peter Loewen, Pharm.D.

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The Journal of Informed Pharmacotherapy

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Last changed: December 20, 2002

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Re: Test Message *Dr. Peter Jewesson 21 Oct 1999*

Prophylactic anti-emetics *Dr. Peter Jewesson 20 Oct 1999*

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Test Message

From: Peter Loewen

Date: 20 Oct 1999

Time: 20:28:45

Remote Name: border1.vanhosp.bc.ca

Comments

Test message

Last changed: December 20, 2002

Discussion

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Re: Test Message

From: Dr. Peter Jewesson

Date: 21 Oct 1999

Time: 15:07:23

Remote Name: border1.vanhosp.bc.ca

Comments

Test message read.

Last changed: December 20, 2002

Discussion

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Prophylactic anti-emetics

From: Dr. Peter Jewesson

Category: Category 1

Date: 20 Oct 1999

Time: 03:39:05

Remote Name: proxy2-external.crdva1.bc.home.com

Comments

Is there any data to support the use of prophylactic peri-operative anti-emetics for select patients? Can you point me to a good review article?

Last changed: December 20, 2002

Incorrect Text

In the Original Research article entitled "Stability of Domperidone in Extemporaneously Compounded Suspensions" published in The Journal of Informed Pharmacotherapy 2002;8:100-104 an error had occurred regarding the domperidone product used in the study. Under the Methods section, subsection Preparation and Evaluation of Suspension, the first sentence should read "Domperidone suspensions (1 and 10 mg/mL) were prepared in triplicate from commercially-available tablets of domperidone maleate (**Novo-domperidone**[®], Novopharm, Scarborough, Ontario), containing domperidone 10 mg per tablet, and mixed with equal parts of Ora-Sweet[®] and Ora-Plus[®] (Paddock Laboratories Inc., Minneapolis, MN, lots OE6324 and OH6525, respectively)."

[View the Evidence Based Review Article](#)

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Journal of Informed Pharmacotherapy 2002;9 (Apr-Jun)

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Email to the Editors

- Readers respond to "Pharmacist Scope of Practice: A Response to the 2002 ACP-ASIM Position Paper"



Evidence-Based Snapshots with emphasis on rapid review of results

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- Major Cardiovascular Events in Hypertensive Patients Randomized to Doxazosin or Chlorthalidone - The Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT)
- Effect of an ACE-inhibitor, Ramipril, on Death from Cardiovascular Causes, MI and Stroke in High Risk Patients (HOPE trial)

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Updated
October 08, 2002

Editorial

Redefining and Refining the JIP

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This issue of the JIP signals the launch of two important additions to the content that we will deliver to our readers. The JIP has always aimed to provide rapid, relevant, practical information to pharmacotherapy practitioners and researchers. We believe the launch of the **Technology in Practice Section (TIPS)** and the **Evidence-Based Snapshots** section will make the JIP even more relevant to our readers. In order to help accomplish this task, we are pleased to welcome Robert Balen, PharmD and James McCormack, PharmD to the JIP editorial team.

Technology In Practice Section (TIPS)

"Our Age of Anxiety is, in great part, the result of trying to do today's jobs with yesterday's tools." These words of the distinguished communications theorist Marshall McLuhan were never more true. Today's health care practitioners are being constantly challenged by the increasing volume of health information, the changing technology skills required, and their often unsuccessful attempts at avoiding both information overload and anxiety. Pharmacotherapy practitioners now require a core level of technology competence in order to keep pace with patient needs. We believe that a lack of technology skills can lead to apprehension, information overload and suboptimal patient care.

We agree with a recent editorial by O'Malley (1) in which he states that pharmacists have not been at the forefront of integrating available technologies into their practice settings and that there is a "worrisome" technology gap in our profession. A survey we recently conducted at one of our institutions indicates that the greatest work-related technology challenge that pharmacists perceive is a lack of skills required to effectively use currently available technology and on-line resources for patient care. The vast majority of the respondents believe that their practice effectiveness could significantly increase if their computer, Internet, and information management skills could be improved.

The purpose of the TIPS is to empower readers with the knowledge required to integrate technology into their practice to improve patient care, research, education and life-long learning effectiveness. This section of the JIP will focus on technologies that are currently available, ubiquitous and can be procured "off-the-shelf" by individuals. The TIPS will expand the scope of the "Pharmacotherapy on the Web" section, which has been part of the JIP since its inception. Web site reviews will expand to include resources that provide content on information management and computer skills.

We invite readers to guide the content of TIPS by **submitting questions and topic suggestions**. We want to hear about your technology-related challenges and we plan to provide a forum for addressing some of the questions you send us. We also invite you to submit a description of innovative solutions that you have developed to meet some of these challenges in your practice setting.

TIPS will feature topics such as:

- How to use the Internet to help you keep up with the literature and improve your practice
- How to choose and use a personal digital assistant (PDA) for your practice
- How to manage and organize your professional resource material
- How to make your pertinent resources electronically available to you in your practice area
- How to optimize your internet and medical database search strategies
- How to regain control of your email in-box

Other exciting plans for this section include:

- Critical evaluations of drug and disease information software
- Forums for reader-initiated information exchange
- Tips on knowledge management and knowledge sharing in practice

We look forward to your questions and hearing about your day-to-day technology-related challenges.

Evidence-Based Snapshots

Due to the popularity of the **Evidence-Based Reviews of the Pharmacotherapy Literature** section, we are enhancing this section with more of what our readers want. Our readers have told us that they want the "quick and dirty" details on the flood of new trials that are being reported daily: Details like "Who was studied?", "What were the results?", "What does it mean?" Our goal is to provide a synopsis of these studies **no later than one week** from the time it is released. The section will be called **Evidence-Based Snapshots** and will be introduced over the next few weeks. To illustrate what we intend to provide, some examples of older trials have been published in this issue of the JIP.

We will be relying on our JIP Section editors, and on you to help us by suggesting studies that should be included in this section. Our editors are experts in their therapeutic areas and review the journals pertinent to their expertise on a regular basis. In particular, we are interested in those studies that have the potential to impact on how we use pharmacotherapy to improve patient outcomes. This includes studies involving new therapies, and those that shed more light on how to best use currently available drugs. We will also be soliciting brief commentaries and opinion from other experts. We also invite you to recommend articles which should appear in this section using our **Feedback** form.

It is not our goal to do a formal critical appraisal on each article. Instead, we plan to create a simple synopsis of the findings. A more extensive critical review will continue to be done for selected studies in the **Evidence Based Reviews of the Pharmacotherapy Literature** section.

Ultimately you, the reader, will decide whether these changes to the JIP are meaningful to you. We invite you to let us know what you think of them.

Peter S. Loewen, B.Sc.(Pharm), Pharm.D.

Publishing Editor

Robert M. Balen, B.Sc.(Pharm), Pharm.D.

Associate Editor

James P. McCormack, B.Sc.(Pharm), Pharm.D.

Associate Editor

The Journal of Informed Pharmacotherapy

J Inform Pharmacother 2002;9:1

References

1. O'Malley, CH. Pharmacy and the e-train: Time to get on board. Am J Health-Syst Pharm 2001;58:39.

Reader Responses to the Editorial, "Redefining and Refining the JIP"

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Evidence Based Snapshots

The Journal of Informed Pharmacotherapy 2002;9:150.

Irbesartan and Amlodipine in Patients with Nephropathy due to Type 2 Diabetes

Reviewer: James McCormack, B.Sc. (Pharm), Pharm. D.

Reviewer's email address: jmccorma@interchange.ubc.ca

Reviewer's profession/specialty: Professor, Faculty of Pharmaceutical Sciences, University of British Columbia

Original Citation

Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345:851-60. [PubMed Citation](#)

Overall Study Question

These investigators examined the benefit of treating hypertensive patients with nephropathy due to type 2 diabetes with irbesartan, amlodipine, or placebo.

Patients

1715 hypertensive patients with nephropathy due to type 2 diabetes.

Treatment

Irbesartan 300 mg po daily, amlodipine 10 mg po daily or placebo.

Duration

2.6 years

Results

	Doubling of SCr, ESRD (dialysis, renal transplant or Cr of at least 530 umoles/ L) (%)	ESRD (%)	CV death, MI, CHF, stroke, limb amputation (%)	Serious adverse effects (%)
Irbesartan	32.6	14.2	23.8	61
Amlodipine	41.1	18.3	22.6	
Placebo	39	17.8	25.3	
Relative Risk Reduction (Irbesartan versus Placebo)	16	NSS		
Absolute Risk Reduction	6.4			
NNT/NNH over 2.6 years	16			

NNT = numbers needed to treat, NNH = numbers needed to harm, NSS = not statistically significant

Mean arterial pressure was 3.3 mmHg lower in the drug groups - approximately 3/3 mmHg lower in the drug groups.

How does this study contribute to the drug therapy of hypertensive type 2 diabetics with nephropathy?

This study showed that an angiotensin-II-receptor blocker reduced the chance of the doubling of SCr, ESRD -dialysis, renal transplant or Cr of at least 530 by 6.4% compared to placebo in hypertensive type 2 diabetic patients with nephropathy over 2.6 years.

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Evidence Based Snapshots

The Journal of Informed Pharmacotherapy 2002;9:151

Major Cardiovascular Events in Hypertensive Patients Randomized to Doxazosin or Chlorthalidone - The Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

Reviewer: James McCormack, B.Sc. (Pharm), Pharm. D.
Reviewer's email address: jmccorma@interchange.ubc.ca
Reviewer's profession/specialty: Professor, Faculty of Pharmaceutical Sciences, University of British Columbia

Original Citation

Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). ALLHAT Collaborative Research Group. JAMA 2000;283:1967-75. [PubMed Citation](#)

Overall Study Question

These investigators evaluated the differences in long-term outcomes when hypertensive patients were treated with either doxazosin or chlorthalidone.

Patients

24,335 patients mean age 67 (47% women) with hypertension (>140/90) and at least one other coronary heart disease risk factor.

Treatment

Chlorthalidone 12.5 or 25 mg po daily versus doxazosin 2,4, and 8 mg po daily.

Duration

The doxazosin arm was stopped early after 3.3 years.

Results

	Fatal and nonfatal MI (%)	All deaths (%)	CHD death, non-fatal MI, revascularization, and angina (%)	CHF (%)	Strokes (%)
Chlorthalidone	6.3	9.1	12	4.5	3.6
Doxazosin	6.3	9.6	13.1	8.1	4.2
Relative Risk Reduction	NSS		8	44	31
Absolute Risk Reduction			1.1	3.6	0.6
NNT/NNH over 3.3 years			91	28	167

NNT = numbers needed to treat, NNH = numbers needed to harm, NSS = not statistically significant

Systolic blood pressure was approximately 2-3 mmHg lower in the chlorthalidone group, there was no difference in the diastolic blood pressure between groups. Cholesterol was 0.2 mmol/L lower, potassium was 0.4 mmol/L higher, and mean serum glucose was 0.2 mmol/L lower in the doxazosin group.

How does this study contribute to the drug therapy of patients with hypertension?

This study shows that despite similar changes in surrogate markers, chlorthalidone patients had fewer CHD death, non-fatal, MI, revascularization, and angina (1.1% absolute difference), CHF (3.6 % absolute difference) and strokes (0.6% absolute difference) than patients treated with doxazosin.

Evidence Based Snapshots

The Journal of Informed Pharmacotherapy 2002;9:152.

Effect of an ACE-inhibitor, Ramipril, on Death from Cardiovascular Causes, MI and Stroke in High Risk Patients (HOPE trial)

Reviewer: James McCormack, B.Sc. (Pharm), Pharm. D.

Reviewer's email address: jmccorma@interchange.ubc.ca

Reviewer's profession/specialty: Professor, Faculty of Pharmaceutical Sciences, UBC

Original Citation

Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000;342:145-53 [PubMed citation](#)

Overall Study Question

These investigators evaluated the benefit of treating high risk patients with either ramipril or placebo.

Patients

9,297 patients mean age 66 (26% women) with a history of CAD (80%), stroke (11%), peripheral vascular disease (45%), or diabetes (39%) PLUS AT LEAST ONE OF either hypertension (47%), elevated total cholesterol (66%), low HDL (19%), smoker (14%), or documented microalbuminuria (21%) - excluded if they had heart failure - prior to randomization - run in phase - 2-3 weeks - 1035 of 10,576 dropped out due to noncompliance, side effects, abnormal serum creatinine/ potassium or withdrawal of consent.

Treatment

Ramipril 10 mg PO daily (starting at 2.5mg) or placebo.

Duration

5 years

Results

	MI, stroke, death from CHD (%)	All deaths (%)	MI (%)	Revascularization (%)	CHF (%)	Strokes (%)
Ramipril	14.0	10.4	9.9	16.0	9.0	3.4
Placebo	17.8	12.2	12.3	18.3	11.5	4.9
Relative Risk Reduction	21	15	20	13	22	31
Absolute Risk Reduction	3.8	1.8	2.4	2.3	2.5	1.5
NNT/NNH over 5 years	28	56	43	38	40	67

NNT = numbers needed to treat, NNH = numbers needed to harm

Blood pressure was 3/2 mmHg (2 years) to 2/1 mmHg different at end of trial.

How does this study contribute to the use of ACE inhibitors in high-risk patients?

This study shows that treatment of patients with a history of a cardiovascular complication or diabetes plus at least one other risk factor with ramipril reduces the chance of MI, stroke, death from CHD by 3.8%. Whether this benefit is unique to ACE inhibitors versus other antihypertensives or antihyperlipidemics is not clearly known.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2002;9:200.

Carvedilol for severe chronic heart failure: Centre of the Universe or Just Another Beta-blocker?

Reviewer: Derek Jorgenson

Reviewer's email address: dljorgenson@sympatico.ca

Reviewer's profession/specialty: Pharmacist/PharmD student (University of Toronto)

Original Citation

Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL; Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651-8.

PubMed Citation

Overall Study Question

This randomized, multicentre, double blind, placebo-controlled trial (denoted the “Copernicus” study) was designed to determine the effects of the beta-blocker carvedilol on the survival of patients with severe heart failure as a result of ischemic or non-ischemic cardiomyopathy.

Patient were included in this study if they demonstrated symptoms of heart failure at rest or on minimal exertion, were clinically euvolemic, and had an ejection fraction of less than 25 percent, despite being treated with conventional therapy. Conventional therapy was defined as treatment with diuretics (in a dose which achieved the absence of rales, ascites, and minimal peripheral edema) and an angiotensin-converting-enzyme inhibitor (or an angiotensin II receptor blocker). Treatment with nitrates, hydralazine, digitalis, spironolactone, and amiodarone was allowed, but not required.

There were several exclusion criteria employed in this study. Patients were excluded if they required recent intensive care or intravenous inotropes or vasodilators within four days of screening. Patients were also excluded if they had heart failure as a result of valvular disease, correctible cardiomyopathy, or were likely to receive a cardiac transplant in the near future. Patients were also excluded if they had recently undergone coronary revascularization, experienced an acute MI, stroke, or cardiac arrhythmia. Patients who had received an alpha-adrenergic blocker, a calcium channel blocker, or a class I antiarrhythmic drug within the four weeks, or a beta-blocker within two months, were also excluded; along with patients with a systolic BP <85mmHg, a HR <68bpm, a SCr >247.5umol/L, or a serum potassium <3.5mmol/L or >5.2mmol/L.

Patients meeting study criteria were assigned to receive either oral carvedilol or matching placebo. The dose of each drug was started at 3.125mg po twice daily, and was doubled every two weeks up to a target dose of 25mg twice daily as tolerated by the patient. Doses of all concomitant drugs could be adjusted at the discretion of the investigator. The patients were evaluated every two months until the end of the trial. The primary outcome of the study was death from any cause, and the composite of death or hospitalization for any reason was used as a secondary endpoint.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Patients who met the entry criteria were randomly assigned in a 1:1 ratio to receive either intervention. The study was executed by an independent steering committee who ensured the random allocation of treatments.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. After the trial was discontinued prematurely, the investigators had a mean of 10.4 months of follow-up data for all 2,289 patients who were enrolled. No patients were lost to follow-up. In addition, the primary data analysis was performed on an intention-to-treat basis.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. This was a double-blind trial. Patients, clinicians, and study personnel were blinded to treatment. The trial was designed, executed, and analyzed by a steering committee, an end-points committee, a biostatistics center, and a data and safety monitoring board, all who conducted their roles independently from the sponsors.

4. Were the groups similar at the start of the trial?

Yes. The groups appear to be similar at baseline with respect to disease severity (ejection fraction, previous hospitalizations, blood pressure, heart rate, and serum creatinine) and concomitant treatments (ACE inhibitor, digitalis, diuretic, spironolactone, and amiodarone use). They did not report the proportion of patients receiving ASA and cholesterol lowering therapies; however, considering these patients were extremely high-risk cardiac patients, it might be assumed that most were receiving these therapies. The authors also did not report if the mean dose of ACE inhibitor therapy was equivalent between the groups, which potentially may bias the results; however, the authors addressed this point in a subsequent letter to the editor in which they report that the average doses were indeed similar between groups. (1)

5. Aside from the experimental intervention, were the groups treated

equally?

Yes. Both groups were followed-up at 2-month intervals until the discontinuation of the trial, and fewer than 5% of patients in both groups received open-label treatment with a beta-blocker at some point in the trial.

What were the Results?

1. How large was the treatment effect?

Recruitment was terminated prematurely after a mean follow-up of 10.4 months. This was undertaken when it was determined by interim analysis that the patients in the carvedilol treatment group were having a significant beneficial effect from the intervention compared to the placebo group.

According to the intention to treat analysis, there was a statistically significant benefit in the carvedilol group for the primary outcome of all-cause mortality. The placebo group had 190 of the original 1,133 patients die during the 10-month follow-up, which is a crude mortality rate of 16.8%. The carvedilol group had 130 of the original 1,156 patients die during the same timeframe, which is a crude mortality rate of 11.2%. This represents an absolute reduction in all-cause mortality of 5.6% ($p=0.00013$), a relative risk reduction of 35%, and a corresponding number needed to treat (for approximately 4 months) of 18. According to Kaplan-Meier analysis, the cumulative risk of death at one year was 18.5% in the placebo group and 11.4% in the carvedilol group ($p<0.05$).

A similar beneficial effect was observed for the secondary outcome of the combined risk of death or hospitalization. According to the intention to treat analysis, 44.7% of the patients in the placebo group died or were hospitalized over the 10-month follow-up, compared to 36.8% in the placebo group ($p<0.01$). This represents an absolute reduction of 7.9% (relative risk reduction of 18%) and a corresponding number needed to treat (for approximately 4 months) of 13.

These benefits were seen across all subgroups defined according to sex, age, left ventricular ejection fraction, cause of heart failure, location of study center, and history with respect to hospitalization in the previous year.

The carvedilol also appeared to be better tolerated than placebo, with cumulative withdrawal rates due to adverse effects or for reasons other than death being 18.5% in the placebo group and 14.8% in the carvedilol group ($p=0.02$). It is unexpected, and difficult to rationalize, that the placebo group actually had more withdrawals than carvedilol in this trial. However, this difference could be explained by more patients in the placebo group discontinuing therapy due to poor disease control, as opposed to poor tolerability of the placebo. Unfortunately the authors did not provide specific reasons for drug therapy withdrawal, making it difficult to explain this result. Nevertheless, it is comforting from a clinician's perspective that as many as 85% of patients with severe heart failure will tolerate carvedilol if it is initiated and titrated conservatively.

2. How precise was the estimate of the treatment effect?

The reported confidence intervals were fairly narrow and did not approach zero (no effect). The relative risk reduction of 35% for the primary endpoint of all-cause mortality had a 95% CI of 19 - 48%. This suggests the estimate of the treatment effect was very precise, as the minimal benefit that we could expect according to this trial is still a 19% relative risk reduction in all-cause mortality.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

The results of this study suggest that long-term treatment with carvedilol results in a significant benefit in patients with severe chronic heart failure, regardless of what subgroup they are from. These results can be applied to my patients only to the extent that they would have fit into the rather extensive inclusion/exclusion criteria of this trial. Patients who required intensive care, had marked fluid retention, were receiving IV inotropes or vasodilators, had a recent MI or stroke, were hypotensive, or had severe renal dysfunction were not included in this study. It cannot be assumed that these patients would receive the same benefits from treatment with carvedilol, and therefore should be stabilized before being considered for this therapy. It is possible that in patients who are severely decompensated, activation of the sympathetic nervous system is critical to maintain cardiovascular stability, and administration of a sympathetic nervous system antagonist may not be advantageous.

Interestingly, only 19-20% of the patients were receiving concomitant therapy with spironolactone during this trial. Considering the results of the RALES Trial (2), most of these patients with severe heart failure would benefit from this intervention. Therefore, there is the possibility that these results with carvedilol may not be the same in a present day cohort of patients also receiving spironolactone. However, the RALES Trial did report that the beneficial effects of spironolactone were similar in subgroups of patients who did, and who did not receive concomitant beta-blockers. Also, the authors of the current study reported in their subsequent letter to the editor that a post-hoc analysis of patients who were, and who were not receiving spironolactone, suggested that the benefits of carvedilol were similar in both cohorts.(1) Therefore, we can be fairly confident that the benefits seen with carvedilol in this study can be applied to our severe chronic heart failure patients today, most of whom are receiving spironolactone.

2. Were all clinically important outcomes considered?

The endpoints of mortality and hospitalization were considered, which are the outcomes of clinical importance to patients suffering from severe chronic heart failure.

3. Are the likely treatment benefits worth the potential harms and costs?

Administration of carvedilol in patients with severe chronic heart failure resulted in a relative risk reduction in mortality of 35%, which translated into a number needed to treat of 18 for approximately 10 months to prevent one death, and a number needed to treat of 13 for the same duration to prevent one death or hospitalization. These outcomes are without a doubt very clinically important. The dramatic physical and financial benefits of this reduction in death and hospitalization are realized with very little cost or increased risk. The titration of carvedilol was actually better tolerated in this trial than placebo was, and could likely be done in an outpatient setting, making it safe and inexpensive. However, there were still 15% of the patients in the carvedilol group who could not tolerate the medication, which suggests that even using a very slow dose titration, many patients will not tolerate this therapy.

Commentary

Metoprolol and carvedilol have been demonstrated in earlier trials to be effective in reducing the risk of hospitalization and death in patients with chronic heart failure. (3-5) Unfortunately, these earlier studies primarily involved patients who had only mild-moderate heart failure (i.e. New York Heart Association (NYHA) Class II or III). Consequently, little has been known about the effects of these agents in patients with severe heart failure. This distinction is very significant, and concern has been expressed that beta-blockers may actually worsen the symptoms and prognosis of heart failure, especially in patients with very severe disease. (6) This concern appears to be unfounded in patients with mild-moderate disease, but it remains a valid consideration in patients with severe symptoms. (3-5)

The results of this study are likely to have a profound effect on the treatment of patients with severe heart failure. This trial has demonstrated that long-term treatment of patients with severe heart failure (NYHA Class III-IV symptoms and ejection fraction < 25%) using carvedilol has a significant benefit in prolonging survival and preventing hospitalization. This is the first published study to reveal a beneficial effect using a beta-blocker in severe heart failure, and helps disprove the theory that it may be unsafe to use these drugs in this patient cohort. This study provides a missing piece of the therapeutic puzzle as it relates to beta-blocker therapy in the treatment of chronic heart failure. There is now evidence that, regardless of the severity of the symptoms, patients with heart failure will benefit from beta-blocker therapy. However, future research is still required to determine if the benefits in patients with severe heart failure can be extrapolated to other beta-blockers, and to a cohort of patients who are all concomitantly receiving spironolactone.

When titrated very slowly, carvedilol was found to be better tolerated than placebo in this study; however, a substantial proportion of patients (i.e. 15%) were still unable to tolerate the medication. Therefore, despite the fact that this trial demonstrates that the administration of carvedilol is safe and effective in these patients with severe chronic heart failure, this drug cannot be tolerated by all patients.

The significant question that remains is whether or not these results can be extrapolated to the use of beta-blockers other than carvedilol. As mentioned earlier, metoprolol, carvedilol and bisoprolol have all been shown to be safe and effective in patients with milder disease. (3-5) A recent randomized controlled trial involving an assessment of the long-term effects of bucindolol in patients with severe heart failure showed no significant difference between bucindolol and placebo after ten months of follow-up. (7) This suggests that perhaps the previous beneficial effects seen with metoprolol or

bisoprolol in patients with mild-moderate heart failure cannot be assumed to translate into similar benefits in severe heart failure, as they have with carvedilol.

Carvedilol has been shown to have some pharmacological effects (i.e. alpha-adrenergic blockade, antioxidant effects, antiendothelin effects) in addition to beta-adrenergic blockade. This property does not appear to exist for most other beta-blockers. Since it is not known what the precise mechanism is that leads to the beneficial effects of beta-blockers in heart failure, it is plausible that these unique aspects of carvedilol may translate into an enhanced benefit in patients with severe heart failure. Therefore, based on the lack of evidence with other beta-blockers, and the existing evidence with bucindolol, it should not be assumed that any beta-blocker other than carvedilol is safe and effective in treating patients with severe heart failure. This creates an interesting therapeutic and ethical dilemma when using a beta-blocker other than carvedilol for a patient with mild-moderate heart failure, when we know they will eventually progress to a more severe state, at which time we cannot guarantee the effectiveness of their beta-blocker therapy. These questions and dilemmas will likely be clarified as results of future trials are reported which study the effects of other beta-blockers in patients with severe heart failure.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;9:201.

Warfarin or Aspirin for Recurrent Ischemic Stroke: Prophylaxis WARSS!

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Reviewer's profession/specialty: Clinical Pharmacy Specialist - Internal Medicine

Original Citation

Mohr JP, Thompson JL, Lazar RM, Levin B, Sacco RL, Furie KL, Kistler JP, Albers GW, Pettigrew LC, Adams HP Jr, Jackson CM, Pullicino P; Warfarin-Aspirin Recurrent Stroke Study Group. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med 2001;345:1444-51.

PubMed Citation

Overall Study Question

To determine whether warfarin is superior to ASA for secondary prevention of acute ischemic stroke in patients without atrial fibrillation. The study sample included 2,206 30-85 yr old (mean age 63 yrs) patients with an ischemic stroke (non-cardioembolic, non carotid artery source) during the previous 30 days and either severe, moderate, or no post-stroke disability (92% had minimal or no disability). Patients had no obvious contraindications to warfarin therapy. 68% had hypertension, 33% had diabetes, 28% had known cerebrovascular disease at the time of their index stroke. The primary outcome variable was death from any cause or recurrent ischemic stroke. The secondary outcome variable was major or minor hemorrhage. The study intervention was ASA 325mg once daily or Warfarin titrated to INR 1.4-2.8 (mean achieved 2.1, 70.7% within target range) for 2 years.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. Primary endpoint status at 2 years was established for 98.5% of patients. Only 11 patients withdrew consent and only 22 were lost to follow-up. A total of 3 primary events

occurred during the trial among the patients who were ultimately lost to follow up.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. A double-dummy design was used and double-blinding was maintained by using the same blood monitoring schedule in both groups. INR testing was done by a central laboratory for all patients. Site investigators were sent actual INR results for warfarin-treated patients and false INR results for ASA treated patients, so “warfarin” dosage adjustment was occurring in both groups to maintain the double-blind.

4. Were the groups similar at the start of the trial?

Yes. The two populations were similar for almost all reported baseline characteristics. Of possible significance, the warfarin arm had more diabetics and large artery strokes at baseline (~3% absolute difference for each).

5. Aside from the experimental intervention, were the groups treated equally?

Yes. Appropriate measures were taken to maintain blinding and all other study procedures were identical.

What were the Results?

1. How large was the treatment effect?

Death or recurrent stroke at 2 years was identified in 16% of ASA recipients and 17.8% of warfarin recipients ($p=0.25$). Recurrent ischemic stroke, death or major hemorrhage occurred in 17.8% of ASA patients and 20.0% of warfarin patients (NS). Major hemorrhages occurred in 1.5% of ASA and 2.2% of warfarin recipients ($p=0.1$). Minor hemorrhage was reported in 12.8%/year of ASA patients versus 20.8%/yr of warfarin patients ($p<0.001$). Finally, death due to hemorrhage was identified in 0.4%/yr of ASA patients versus 0.6%/yr of warfarin patients (NS). There were no significant differences among any of the subgroups reported (including location or severity of initial infarct).

2. How precise was the estimate of the treatment effect?

For the primary endpoint, the 95%CI for the hazard ratio (1.13) was 0.92 - 1.38. My calculation of the 95%CI for the absolute risk difference (1.81%, favouring ASA) is 3.12%. This means that the results are consistent with warfarin being superior to ASA by an absolute difference of 1.31% through to warfarin being inferior to ASA by as much as 4.93%. If one arbitrarily assumes a minimally clinically significant ARR difference of 2% (note: using the ASA event rate in this trial, this would be equivalent to as much as a 12.5% relative difference), it is possible that there is ASA is superior to warfarin, or there

no difference between these two drugs . However, warfarin could not be superior to ASA. Conversely, If one sets the minimally clinically significant ARR difference at 5% (i.e. the difference the investigators powered this study to detect), the results are consistent with warfarin and ASA being equivalent. This trial was not set up to demonstrate equivalence of the two treatments, but rather to detect a 30% relative (4.8% absolute) difference in efficacy between them, favouring either treatment.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. This trial was well conducted and the results were appropriately reported.

2. Were all clinically important outcomes considered?

Mostly. A potentially important endpoint not reported was the severity (i.e. the degree of subsequent disability) of the strokes which occurred during the trial. Recent evidence from Wilterdink et al indicates that ASA use at the time of a stroke can result in less severe stroke-related disability. (1) If there were a difference between ASA and warfarin with respect to this parameter, it would be of clinical importance.

3. Are the likely treatment benefits worth the potential harms and costs?

If readers accept that ASA and warfarin are equivalent based on this data (or conversely, that warfarin is potentially inferior), the currently accepted strategy of using ASA alone in this population should remain unchanged.

Commentary

While this trial did not reveal improved outcomes among warfarin-treated patients, it nevertheless provides us with some clinically relevant information.

The finding is that warfarin may be considered an alternative to ASA in ASA-allergic patients for secondary stroke prevention is clinically relevant. Since warfarin would likely be contraindicated in patients with prior ASA-associated PUD/GI bleeding, this would not represent a suitable alternative in this circumstance. Another alternative to ASA would include clopidogrel. Generally, clopidogrel would be favoured over warfarin due to its ease of use and possibly lower cost when monitoring is considered. Thus, warfarin is likely still relegated to 3rd or 4th-line therapy (i.e. after ASA, clopidogrel, ASA plus dipyridamole, and possibly ticlopidine) in this population, just as it was before this trial, except that now data is available to support its use at all, whereas before none was available.

This study would also suggest that newly diagnosed stroke patients who are receiving warfarin for another indication (e.g. post-anterior MI thrombosis prophylaxis) may not require the addition of ASA to their drug regimen. Warfarin alone should be effective for stroke prophylaxis in this setting.

While the possibility that the finding that INR <2.0 was not as protective as INR >2.0 in this trial is intriguing, this must be allayed by the finding that no differences (or even a trend toward differences) were observed over the range of INR of 1.5 to >3.0.

Finally, this trial does not address the question of whether combination low-INR warfarin plus ASA is superior to either alone in this patient population. The SPIRIT trial showed increased major bleeding among patients treated with ASA plus higher intensity warfarin for the same indication. (2) Regardless, any regimen involving adjusted-dose warfarin would likely be more monitoring-intensive and therefore more expensive than antiplatelet therapy alone.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;9:202.

Amiodarone in Cardiac Arrest: Barely ALIVE and Kicking?

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Reviewer's profession/specialty: Pharmacotherapeutic Specialist - Emergency Medicine

Original Citation

Dorian P, Cass D, Schwartz B, Cooper R, Gelaznikas R, Barr A. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. N Engl J Med 2002;346:884-90. [PubMed Citation](#)

Overall Study Question

The ALIVE study was conducted to determine the efficacy of intravenous (IV) amiodarone compared with lidocaine for the management of patients with out-of-hospital cardiac arrest due to shock-refractory ventricular fibrillation (VF). Adults with non-traumatic out-of-hospital cardiac arrest were eligible for the study if VF persisted after three shocks from an external defibrillator, a single dose of IV epinephrine, and a fourth defibrillator shock, or if they had recurrent VF subsequent to successful defibrillation. The primary endpoint was survival to admission to the hospital intensive care unit (ICU). The secondary endpoints included survival to hospital discharge and adverse events, defined as the need to administer dopamine or atropine after administration of the study drug.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

All patients received epinephrine 1 mg IV and were then randomized to receive amiodarone 5 mg/kg IV or lidocaine 1.5 mg/kg IV. If VF persisted after a further shock, a second dose of the study drug was administered (amiodarone 2.5 mg/kg or lidocaine 1.5 mg/kg) and attempts at resuscitation were continued.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

347 patients met inclusion criteria and were randomized to receive amiodarone (N=180) or lidocaine (N=167). All patients were included in the final analysis.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

The study was blinded using a double-dummy technique. Patients received amiodarone 5 mg/kg IV (or matching placebo containing the same diluent (polysorbate 80) diluted in 30 mL of D5W) or lidocaine 1.5 mg/kg IV (or its matching placebo). If VF persisted after a further shock, a second dose of the study drug or matching placebos were administered.

4. Were the groups similar at the start of the trial?

The baseline characteristics of the amiodarone and lidocaine groups were similar.

5. Aside from the experimental intervention, were the groups treated equally?

There were no differences in the further treatment of patients assigned to amiodarone or lidocaine.

What were the Results?

1. How large was the treatment effect?

The primary endpoint of survival to hospital admission was observed in 22.8% patients treated with amiodarone as compared to 12% of patients who received lidocaine, (odds ratio [OR] 2.17, 95% confidence interval [CI] 1.21-3.83, $p=0.009$). This correlates to an absolute risk reduction (ARR) of 10.8% and a number needed to treat of 10.

The secondary endpoint of survival to hospital discharge was observed in 5% and 3% of patients in the amiodarone and lidocaine groups, respectively, ($p=ns$). Overall, only 4% of all patients in the study survived to hospital discharge.

There was no difference between the amiodarone and lidocaine groups regarding the proportion of patients who needed treatment for bradycardia with atropine (24% vs. 23%) or pressor treatment with dopamine (7% vs. 4%).

2. How precise was the estimate of the treatment effect?

The 95% CI for the primary endpoint of survival to hospital admission do not include zero, indicating statistical significance (OR 2.17, 95% CI 1.21-3.83, $p=0.009$).

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

The use of intravenous amiodarone in patients with out-of-hospital cardiac arrest due to shock-refractory VF amiodarone is more effective than lidocaine in achieving survival to hospital admission. However, the external validity to patients who experience an in-hospital VF arrest remains unclear.

2. Were all clinically important outcomes considered?

Although the ALIVE trial was able to demonstrate a benefit in the surrogate endpoint of survival to hospital admission, the trial was underpowered to evaluate the more clinically relevant endpoint of survival to hospital discharge. In addition, the trial was also underpowered for the purpose of evaluating the relative effect of amiodarone vs. lidocaine on the functional neurological status of survivors upon discharge from hospital.

3. Are the likely treatment benefits worth the potential harms and costs?

Many questions still remain unanswered regarding the use of intravenous amiodarone in patients with cardiac arrest due to shock-refractory VF. In a trial which failed to demonstrate a survival benefit and demonstrated an overall survival of only 4%, the economic implications of using a more expensive agent (amiodarone) to a less expensive alternative (lidocaine) needs to be further evaluated. In addition, when considering the increased admission to hospital but poor overall survival of these patients, it is apparent that an economic evaluation involving of the cost of care should be undertaken.

Commentary

Although the use of lidocaine or amiodarone is recommended in the ACLS treatment guidelines for VF arrest, the evidence supporting the use of antiarrhythmic therapy has not been clearly established in clinical trials. (1) The ALIVE trial follows on the heels of the ARREST trial which compared amiodarone to placebo in out-of-hospital VF or pulseless ventricular tachycardia. (2) While the ARREST trial was an important trial in the continuum of resuscitation research, this investigation fell short in providing any clear guidelines for use of amiodarone in clinical practice as a result of the placebo controlled design and the insufficient statistical power to demonstrate an overall survival benefit. Although survival to hospital admission was found to be improved in amiodarone-treated patients in ALIVE and ARREST, the absolute benefit of 10% (NNT = 10) was identical in both trials. However, this surrogate endpoint did not appear to correlate to improved overall survival. As the study was underpowered to make any firm conclusions on overall survival and functional neurological status, a larger trial is clearly required to evaluate these endpoints.

The authors of the ALIVE trial conclude that "...on the basis of these results, and the accumulated evidence from previous trials, there appears to be no indication for the administration of lidocaine to patients with shock-refractory ventricular fibrillation in the out-of-hospital setting. We believe that if an antiarrhythmic drug is to be considered in this situation, intravenous amiodarone should be the drug of choice." While it is clear that the evidence supporting the use of lidocaine in shock-refractory VF arrest is weak; one could also argue that the evidence for amiodarone is not much better. Should we administer amiodarone to patients if this drug improves the likelihood of arrival alive to the hospital,

even if more than 95% of these patients succumb before discharge? What about the external validity to in-hospital VF arrest where the endpoint used in both ALIVE and ARREST have already been achieved? What about the economic implications of widespread use of amiodarone in all out-of-hospital VF arrests? Based on the doses of study drug used in ALIVE implementation of amiodarone as the agent of choice in VF arrest would cost approximately \$150 CAN for a 70 kg patient treated, as compared to \$8 CAN in drug acquisition costs for lidocaine. This excludes the additional costs of caring for those patients who were admitted to hospital after receiving amiodarone. This increased economic impact on an already burdened healthcare system needs to be further evaluated.

Clinicians should be cautious in the use of amiodarone in the setting of VF arrest until further research is completed to evaluate the efficacy of drug on overall survival, and a clear assessment of the economic impact of preferentially using amiodarone for all out-of-hospital VF arrest has been established.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2002;9:203.

Risperidone or Haloperidol for Schizophrenic Patients: What Does a Focus on Relapse Rate Reveal?

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Original Citation

Csernansky JG, Mahmoud R, Brenner R; The Risperidone-USA-79 Study Group. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. N Engl J Med 2002;346:16-22. [PubMed Citation](#)

Overall Study Question

The objective of this trial was to compare risperidone to haloperidol for reduction of relapse in outpatients with schizophrenia or schizoaffective disorder.

Patients included in the study were adults with clinically stable schizophrenia (82%) or schizoaffective disorder (18%). Patients had to have experienced outpatient crisis management, and treatment in a psychiatric hospital or emergency room within 24 months of study entry. Patients were taking a stable dose of antipsychotic medication for ≥ 30 days, and were judged as clinically stable by investigators. Patients were excluded from the study if they had another primary psychiatric disorder, a personality disorder, a history of refractoriness to antipsychotic drugs, or treatment with depot neuroleptics.

Patients were randomized to receive haloperidol or risperidone. Over seven days the dose of previous antipsychotic medication was decreased as the dose of study medication increased. Doses were increased to 4 mg of risperidone or 10 mg of haloperidol over three days. Starting on day eight, doses were adjusted by investigators to target daily doses of 5-20 mg of haloperidol or 2-8 mg of risperidone.

Primary outcomes were relapse rate and time to first relapse. Secondary outcome measures included: Positive and Negative Syndrome Scale (PANSS) score and subscale scores and adverse effects as assessed by physical exam, laboratory screening and the Extrapyramidal Symptom Rating Scale.

Patients were assessed every week for four weeks, and then every four weeks until all patients had completed one year of treatment.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Patients were randomly assigned to receive haloperidol or risperidone. Details of the randomization procedure were not provided.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. A total of 397 patients were enrolled. Patients who were assessed at least once (N=365) were included in Kaplan-Meier analysis of relapse rate.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. The study was conducted in a double-blind manner. Tablets were identical appearing in order to maintain blinding. Investigators did not report the effectiveness of blinding. It is assumed that this was not evaluated.

4. Were the groups similar at the start of the trial?

Yes. Both groups had similar baseline demographics including DSM-IV diagnosis, and total and subscale scores on PANSS. Since group size was reasonably large and allocation was random, it is unlikely that the two groups would have been different in this regard.

5. Aside from the experimental intervention, were the groups treated equally?

Yes. There was no difference in compliance as assessed by pill counts (97% in the risperidone group and 96% in the haloperidol group).

What were the Results?

1. How large was the treatment effect?

Patients were followed for a median of 364 days (range 3 to 799) in the risperidone treatment group and 238 days in the haloperidol group (range 4 to 794). The mean doses were 4.9 ± 1.9 mg of risperidone and 11.7 ± 5.0 mg of haloperidol. At the end of the study, 25.4% of patients in the risperidone group had relapsed and 39.9% of patients in the haloperidol group had relapsed, ARR = 14.5%, NNT = 9. The Kaplan-Meier estimate of the risk of relapse at the end of the study was 34% for the risperidone group and 60% for the haloperidol ($p < 0.001$), ARR = 26% (95% CI 13.8% to 38.3%), NNT = 4 (95% CI 3 to 8). In

other words, nine patients would have to be tried on risperidone and four patients would have to comply with risperidone for one year instead of haloperidol in order to prevent one relapse. Although the Kaplan-Meier estimate is less conservative, it reflects the favorable tolerability profile of risperidone.

A greater proportion of patients receiving haloperidol discontinued therapy for reasons other than relapse as compared to patients receiving risperidone, (44.1% and 52.7% respectively) relative risk 1.52 (1.18-1.96).

Patients randomized to risperidone experienced small improvements in PANSS scores as compared to haloperidol, however the differences were small and of minimal clinical significance.

There were similar overall incidences of adverse effects in both patient groups (90% in the risperidone group and 91% in the haloperidol group). Patients in the risperidone group gained an average of 2.3 kg, while patients in the haloperidol lost 0.73 kg ($p < 0.001$). There was a greater incidence of extrapyramidal side effects in the haloperidol group as compared to the risperidone group. Patients in the risperidone group improved from baseline, while patients in the haloperidol showed slight worsening on the Extrapyramidal Symptom Rating Scale ($p=0.02$). Fewer patients in the risperidone group required antiparkinsonian medications for more than 30 consecutive days than in the haloperidol group (9% vs. 17.2%, respectively $p=0.02$).

2. How precise was the estimate of the treatment effect?

The risk of relapse at the end of the study for the risperidone group was estimated to be 34% (95% CI 28% to 43%) and for the haloperidol group was 60% (95% CI 50 to 70%). The 95% confidence intervals for the ARR of 26% are 13.8% to 38.3%.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

This trial indicates that stable, medication-compliant outpatients with chronic schizophrenia or shizoffective disorder have a better chance of remaining relapse-free over a period of one year if maintained on risperidone as compared to haloperidol.

2. Were all clinically important outcomes considered?

The primary outcome was clearly defined and is of clinical importance in the long-term management of psychiatric patients. Possible clinically important outcomes that were not considered include quality of life and costs.

3. Are the likely treatment benefits worth the potential harms and costs?

This study shows a reduction in relapse rate for the treatment of schizophrenia with risperidone as compared to haloperidol, with fewer extrapyramidal adverse effects, but greater incidence of weight gain. The full impact of the risk of antipsychotic-induced weight gain on cardiovascular morbidity and mortality has yet to be fully described.

Although the acquisition cost of risperidone is greater than that of haloperidol (approximately 65 times), the decrease in relapse rate would likely trivialize the acquisition cost difference. A pharmacoeconomic evaluation has shown that risperidone does not increase, and may reduce costs of the treatment of schizophrenia through a reduction in hospitalizations as compared to conventional neuroleptics.(1)

Commentary

Risperidone has been compared to haloperidol in many short term and few long term (>1 yr) studies in patients with schizophrenia. (2) As compared to conventional antipsychotics (most commonly haloperidol), risperidone has shown to be beneficial in terms of clinical improvement, with a lower incidence of movement disorders, somnolence, greater patient acceptability, (2) but greater incidence of weight gain. (2,3) Usual study endpoints include symptom and adverse effect scales, as well as clinical global improvement scores. (2) Few studies have assessed relapse rates.

This study offers a unique perspective owing to its long-term follow-up and focus on relapse rate, rather than clinical symptoms as a primary endpoint. The breakdown of the relapse endpoint would have been useful information to report. For example, it would have been interesting to determine how many patients in each group experienced a need for hospitalization, as compared to a worsening of symptoms.

A limitation to the interpretation of this study is the high rate of withdrawal. Despite the fact that doses were adjusted according to response and adverse effects, it has been suggested that the dose of haloperidol is higher than what is generally recommended, and that this may be a factor contributing to the tolerability, effectiveness, and relapse rate observed. (4,5)

Overall, this study indicates that risperidone is associated with a lower risk of relapse than is haloperidol for outpatients with stable schizophrenia or schizoaffective disorder over one year.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;9:400.

An Assessment of the Affiliation Between Authors and Sponsors of Published Clinical Trials Over a 20-Year Period: An Unhealthy Alliance?

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University of British Columbia Pharmacy 405 (Directed Studies) Research Presentation Seminar (Podium presentation). Vancouver, British Columbia, Canada. December, 2001. (Unfunded study).

Context

The pharmaceutical industry has become a major source of funding for biomedical research. Investigators are now required by many journals to declare in writing any potential conflict of interest that may threaten their impartiality. While we fully support the need to disclose relationship details that would not otherwise be obvious to the readers, we are also interested in author-sponsor relationships that would constitute direct and irrefutable conflicts of interest. It has been our general observation that sponsoring company employees have been appearing as co-authors of these publications with increasing frequency.

Objectives

The primary objective of this study was to characterize author-sponsor affiliation trends over time. Secondary objectives include assessments of research funding overall and with respect to time, author affiliations per journal over time and clinical outcomes per funding type over time.

Design

Author-industry affiliations were analyzed for 500 randomly selected clinical trial publications appearing in 5 influential medical journals over a 20-year period. For each journal, 10 randomly selected issues in a given year were scanned to identify papers meeting the publication inclusion criteria. For those papers meeting these criteria, 5 articles per journal-year were randomly selected and reviewed. Information regarding author affiliations, study drug funding sources, study outcomes and other factors was recorded.

Results

Industry provided funding, solely or in part, for 36% of the 500 clinical trials analyzed. Peer-review funding was identified in an additional 36% of the studies, whilst the remainder had no funding source declared. The number of industry-sponsored trials increased over the 20-year period of the study to a maximum of 69% of all trials reviewed for the final 4-year period reviewed (1997-2000). The number of peer-review funded trials remained constant (~20% of total studies reviewed), while the incidence of studies with no funding declaration declined with time. Author affiliation with industry increased from under 10% to a high of 66% in the final 4-year period for those trials with industry as the sole funding source. Over the 20-year study period, an increase in the incidence of studies with author affiliation with an industry sponsor over time was observed for all five journals reviewed. This increase was greatest with the Annals of Internal Medicine, Journal of the American Medical Association, and New England Journal of Medicine. Regardless of funding source, the majority of clinical trials published in the five journals reviewed demonstrated clinical outcome results that favoured the study drug. Over the 20-year period, the incidence of trials reporting positive outcomes for the study drug modestly increased for both industry sponsorship groups, while the reverse was observed for the peer-review and unfunded groups.

Conclusions

To our knowledge, this is the first published report to characterize author-sponsor affiliations according to funding source and time. Our results indicate that pharmaceutical industry sponsored trials are common and have increased in incidence over the past two decades. Our study indicates that author-sponsor affiliations are also common, and have increased during this same time period. These increases in industry involvement increase the potential for bias in clinical trial publications.

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Technology in Practice

How to Use Email and the Internet to Help You Keep Up With the Literature: Part I

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J Inform Pharmacother 2002;9:500.

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Introduction

The proliferation of the "evidence-based" practice paradigm and the pharmaceutical care practice model requires adeptness at navigating an unprecedented volume of literature. According to the National Library of Medicine, an estimated 10,000 completed references are now added to the MEDLINE database on a weekly basis.⁽¹⁾ In addition to MEDLINE, there are other online databases such as EMBASE, HEALTHSTAR and the International Pharmaceutical Abstracts, as well as the internet in general. This information is available to both the healthcare professional and the general public. An increasingly informed healthcare consumer places yet a further demand for the pharmacist to continue to be up to date with healthcare information.

Keeping current with the health sciences literature is an everyday challenge that many healthcare professionals face. This undertaking, although potentially daunting, is necessary for optimal patient care. Some professionals already have a good surveillance approach to the literature, but most probably have a desire to further improve their skills.

Personally, I can recall many times during my two years as a Doctor of Pharmacy student, where I would encounter a role model pharmacist who always seemed to have relevant citations or articles in their files to support the clinical or educational issue at hand. Often these papers came from a wide assortment of journals, some were recent and some were "classics". What did these elite professionals do to keep their knowledge and their personal reference files so complete and up to date? They must have spent hours reviewing the literature and reading the articles, or so it seemed. What these pharmacists had, in fact, was "a system". The system was comprised of an approach to life-long learning, a case-by-case, patient-oriented method of acquiring resources, and a knowledge of how to make technology work for them.

This article is the first of a multi-part series that will review a number of methods whereby healthcare professionals can use the Internet and email to help them to keep up with professional literature. Part one of the series will outline how journal contents can be delivered to you by email. Subsequent installments will review other technology-based surveillance strategies for keeping aware of professional publications. These strategies include using on-line abstracting services; the PubMed search engine, and on-line journal clubs.

Required Computer Skills

Some basic computer skills are required in order to incorporate the strategies discussed in this review. Users will need to be email literate and know how to use an Internet browser such as Netscape or Internet Explorer. Some basic internet search engine techniques will also be needed.

Step 1. Pick Your Sources

Experienced pharmacists may already have a core set of journals that they follow in order to keep up to date with developments in their practice area. New clinicians, or pharmacists who are new to a particular clinical practice area, will first need to decide what information sources are available to them. For example, a new graduate responsible for providing pharmaceutical care to patients in a general medicine practice environment has several key publications to be aware. Information that may impact pharmacotherapy may be provided by a core set of professional journals. An example of a core set of journals that may be of relevance to pharmacists practicing in a broad spectrum of practice areas is provided in Table I.

Table I. Example Core Professional Journal Set for Keeping Up with Developments in Pharmacotherapy

Publication	Internet URL
American Journal of Health System Pharmacists	http://www.ashp.org/public/pubs/ajhp/
Annals of Pharmacotherapy	http://www.theannals.com/
Pharmacotherapy	http://www.accp.com/pharmacotherapy.html
Annals of Internal Medicine	http://www.annals.org/
British Medical Journal	http://bmj.com/
Clinical Infectious Diseases	http://www.journals.uchicago.edu/CID/home.html
Journal of the American Medical Association	http://jama.ama-assn.org/
New England Journal of Medicine	http://content.nejm.org/
Journal of Informed Pharmacotherapy	http://www.informedpharmacotherapy.com/

Step 2. Automate the Table of Contents Delivery

Once core resources have been identified, the publishers' internet site can be reviewed to investigate whether or not an automated e-mail table of contents (an "eTOC") delivery service is available. E-mail table of contents is a process whereby the full issue table of contents is delivered from the publisher to the recipient by e-mail. For the Journal of Informed Pharmacotherapy, simply click on the [Elert](#) service icon at the top right corner of the opening screen, or in the left border index, for each issue (Figure 1)

Figure 1. Subscribing to the Journal of Informed Pharmacotherapy Email table of contents (Elert) service

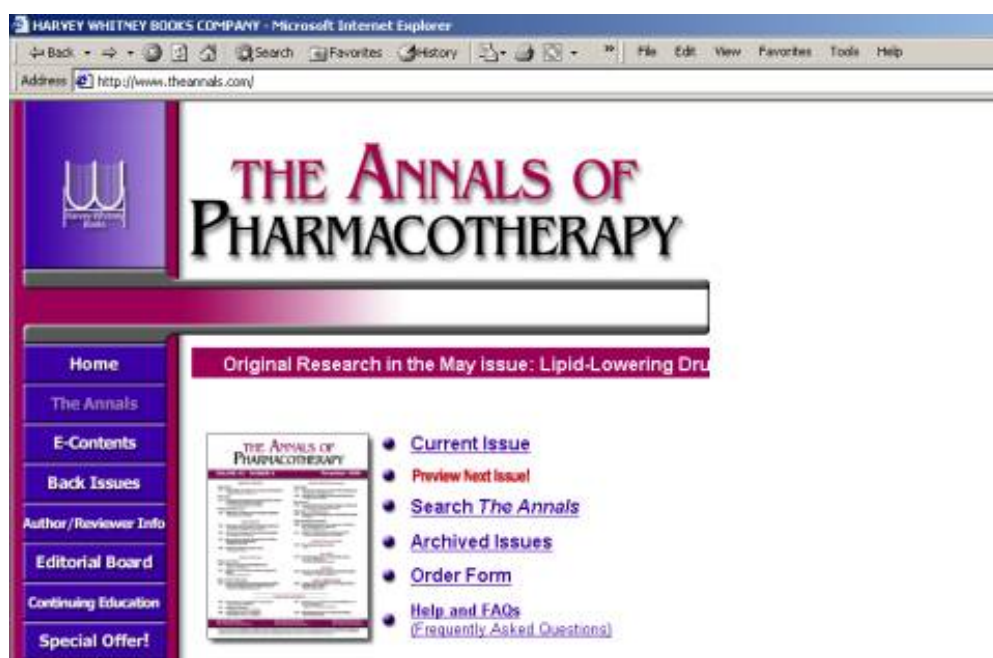


For additional journals, the publishers website can be located by typing in the journal name into an Internet search engine such as [Google](#). For example, in order to locate the Internet site for "[Annals of Pharmacotherapy](#)", type the journal name into the [Google](#) search bar. The appropriate link should appear at or near the top of the search results page (Figure 2). Follow the desired link to the Journal site. Once the publishers web page is in view, look for a link to a table of contents feature as shown in figure 3. Often the link will have a name such as econtents, elert, or customized alerts to suggest that contents are deliverable by email. This process can be repeated for all the journals that you wish to receive the eTOC.

Figure 2. Finding a Professional Journal Website with an Internet Search Engine



Figure: 3 The Annals of Pharmacotherapy E-mail Table of Contents Service. Note the "E-Contents" link in the left side column menu.



Step 3. Check Your Email

Once eTOC subscriptions have been activated, delivery of journal table of contents will begin to arrive by e-mail according to publisher

release schedule (e.g. weekly for the [New England Journal of Medicine](#)). In order to avoid excessive email inbox clutter, subscribers should consider making a dedicated folder or "mailbox" to store eTOC mailings. These e-mails can then be reviewed when time permits. The help section of most e-mail software can provide instructions as to how to set up mailboxes or mail folders to store messages. Also, mail software filtering rules can be applied to automate the transfer of eTOC messages to specified mail folders. Making a habit of scanning through available eTOC is an efficient way to keep up to date with what is coming out in the health sciences literature. Selective reading of articles that are likely to impact practice will help subscribers remain current with advances in pharmacotherapy.

Conclusion

Keeping up to date with professional literature by paper-based means can be a daunting challenge. Advances in information technology make the surveillance of health science publications convenient and manageable. Subscribing to the eTOC service that some journal publishers provide is one strategy that can help health care professionals keep up to date with new developments in their practice area. The advantages of this literature surveillance technique are that information delivery is automated and available for viewing when the recipient chooses. No additional steps beyond opening an e-mail message are required in order to access the journal contents listings. Pre-requisites for using this strategy are access to an internet connected computer, an e-mail account, and familiarity with how to use an internet browser and e-mail software. Not all journals provide an eTOC option. For example, from within the previously identified "core journals", neither the [American Journal of Health Systems Pharmacists](#) nor [Pharmacotherapy](#) offer such a service. The next article in the series will discuss strategies to keep up to date with professional publications that do not have eTOC.

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Journal of Informed Pharmacotherapy 2002;10 (Jul - Sep)

Editorial

- Direct-to-consumer promotion of prescription drugs: should product manufacturers just stick to toothpaste, trucks and tampons?
Peter J. Jewesson



Email to the Editors

- Readers respond to "Direct-to-consumer promotion of prescription drugs: should product manufacturers just stick to toothpaste, trucks and tampons?"

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- Symptom-Triggered vs. Fixed-Schedule Doses of Benzodiazepine for Alcohol Withdrawal
- The Effect of a Proton Pump Inhibitor on the Development of Ulcer Complication Recurrences in Patients taking 100 mg ASA Daily **[corrected text 9AUG02]**
- Risks and Benefits of Estrogen plus Progestin in Healthy Postmenopausal Women (Women's Health Initiative) **[corrected text 9AUG02]**
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Updated
September 12,
2002

Editorial

Direct-to-consumer promotion of prescription drugs: should product manufacturers just stick to toothpaste, trucks and tampons?

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As recently described by Rosenthal et al (1), spending on prescription drugs has now become the fastest growing component of the health care budget. While her comments were aimed at the U.S. market, this phenomenon is one of worldwide significance.

One factor that is probably contributing to this increased spending is direct-to-consumer (DTC) advertising. As aptly coined by Leacock almost 80 years ago, advertising is “superior to reality” and involves “...the science of arresting human intelligence long enough to get money from it...”. (2) And what better targets for advertising than health care and prescription drugs, as so many of us have become, to various degrees, “healthy hypochondriacs” (3) who spend inordinate amounts of unproductive time worrying about things that we often cannot change. As Moynihan et al (4) describe, DTC advertising of prescription drugs is driven in part by the recognition that substantial profits can be made from healthy people who can be made to believe they are sick.

The spending on DTC advertising in the US alone was reported to be about \$2.5 billion in 2000, and this represents a 300% increase over the preceding 4 years. To put this into context, this represents only 15% of the total funds spent on drug promotion in the United States. (1) By comparison, the total research and development expenditures reported by all companies in Canada for 2001 was only \$1.06 billion CAN (~\$0.7 billion US). (5)

So why does industry spend ever increasing amounts of money on DTC advertising of prescription drugs? Because it works. Patients who are exposed to DTC advertising request more advertised drugs, and these products are prescribed even when recognized by physicians as not necessarily being the treatment of choice. (6) DTC advertising is expensive, so manufacturers carefully determine how much money to spend on this form of product promotion on the basis of the number of potential customers, the estimated proportion of these customers that might be persuaded to use their product, the volume of physicians that are likely to prescribe that drug and the monetary return per prescription. The latter is at least partially based upon intended duration of therapy. The longer the customer needs to use the product, the greater the return.

And what drugs do manufacturers typically aim their resources at? As Mintzes points out, the products of interest are new expensive drugs intended for chronic use by a large population of patients. (7) In 2000, 20 drugs accounted for about 60% of the total US spending on DTC advertising. (1) Included in the target list were drugs aimed at weight loss, erectile-dysfunction, birth control, genital herpes and toenail fungal infections. What an intriguing mix of pharmaceuticals, and an interesting commentary about the ailments of our society.

So what's wrong with advertising a product to the people who are ultimately going to consume it? After all, isn't that what free enterprise is all about? Let's list some of the possible pros and cons.

Pros

- DTC advertising may lead to a more health conscious, informed and empowered public (8,9)
- DTC advertising may reduce underdiagnosis and undertreatment of diseases (10)
- DTC advertising may result in earlier management of more serious, costly conditions that consumers typically ignore, or chose not to treat when symptoms appear to be minor or non-acute (7,9)
- DTC advertising information may increase the dialogue between patient and health care workers about drugs and medical conditions (8,11)
- DTC advertising may encourage compliance with prescription drug treatment regimens (12)

Cons

- DTC advertising may result in the promotion of emotional, rather than educational content (13)
- DTC advertising may lead to medicalisation of normal human experiences and disease mongering, resulting in increased use of drugs in healthy patient populations (4, 7)
- DTC advertising may stimulate inappropriate prescribing (9)
- DTC advertising may contribute to an undesirable shift in the relative use of prescription drugs versus over the counter products and non-drug therapies (7)
- DTC advertising may lead to the increased use of drugs for the prevention of medical problems, even when the risk of contracting the medical problem is low and possibly less serious than the adverse effects (both physiological and economic) of the drug itself (7)
- DTC advertising may involve the provision of imbalanced information that leads to erroneous perceptions and "glamorization" of the benefits of a particular drug, while downplaying the potential complications (8)
- DTC advertising may contribute to the increased treatment of poorly correlated surrogate endpoints rather than the targeting of meaningful clinical endpoints (7)
- DTC advertising may result in patients requesting a specific medicine that has been advertised, even though this is not necessarily the best choice (8)
- DTC advertising may produce a negative effect on the pharmacist/patient and doctor/patient relationships by creating conflicts between the patient's desire and the caregivers more informed judgement (8)
- DTC advertising may result in higher costs of care, without necessarily improving quality of life (9)

As stated by Mintzes (14), the question is not whether consumers should obtain information about treatment options; the question is whether drug promotion can provide the type of information consumers need. DTC advertising, in all its direct and indirect forms, is not going to cease...it is just going to become a little more sophisticated, a little more stealthy.

Where do I personally stand on this issue? Overall, I'm not in favour of it. While there may be some benefits related to increased health awareness and enhanced communication with health care professionals that may result from DTC advertising, there are certainly better ways to addresses these

important issues without inviting the fox into the henhouse. Separating drug fact from fiction is something we health care professionals struggle with everyday, and most patients just don't have the tools to compete with the manufacturers in this regard. I suspect there is a net negative impact associated with the promotion of prescription drugs directly to the public. I continue to believe that patients should seek prescription drug information from objective and qualified sources who have no vested interest in the sales of a particular product. This excludes the manufacturers, and unfortunately, the occasional health care professional. As I have already stated, advertising costs money. A lot of money. Wouldn't it be great if the manufacturers redirected these funds towards reduced drug prices, or even better, drug research and development? Now that's a novel idea...and what an advertising gimmick that could be in itself.

I would be very interested in your opinions on this subject. In the interim, consumer beware.

Peter J. Jewesson, PhD FCSHP
Publishing Co-Editor

J Inform Pharmacother 2002;10:1

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Reader Responses to the Editorial, "Direct-to-consumer promotion of prescription drugs: should product manufacturers just stick to toothpaste, trucks and tampons?"

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To the Editors:

I strongly agree with Dr. Jewesson's conclusion that, all things considered, DTCA has a negative impact on society. In my opinion, the cons of DTCA far outweigh the pros. As a pharmacist involved in the increasingly difficult, if not impossible, job of containing runaway drug costs at our 400-bed community hospital, I believe the single factor that tips the argument against DTCA is its effect on the growing costs of health care. These swelling health costs are being fueled to a large extent by the escalating expenditures on pharmaceuticals. According to the Canadian Institute for Health Information, \$12.3 billion was spent on prescription drugs in Canada in 2001. This was 10.6 % more than the previous year and 50 % more than in 1996. Expenditure on drugs has outstripped inflation and total health spending for more than 15 years. Drugs account for 15.2 cents of every health-care dollar, more than is spent on physicians. What has this increase in expenditures purchased? If the additional costs were associated with a flood of innovative, life-saving drugs, they may be justified. However, a recent analysis by the National Institute for Health Care Management (NIHCM) found that of the 1,035 new drugs approved by FDA in the 12-year period from 1989 to 2000, only 153 (15%) were considered "highly innovative". Most of the new drugs were categorized as "incrementally modified drugs" or, more accurately, me-too drugs. And it is these new me-too drugs such as Clarinex and Nexium (replacing the off-patent or soon-to-be off-patent drugs Claritin and Losec respectively) that are mainly being promoted via DTCA in the U.S.

Consumers are being baited into paying for these new, expensive drugs when they have not been shown to be any more effective or safer than the older drugs. It is unfortunate that we will probably never see an advertisement for a more cost-effective generic drug or see balanced ads providing objective information on all available therapeutic options for a given disease or condition. But, as damaging as I believe DTCA is, it is just a small component of a powerful and escalating influence by the pharmaceutical industry on the over-all use of and expenditures on drugs. At the risk of being labeled conspiratorial, I believe that the drug industry is an immense cartel, with enormous control over products that are fundamental to public health. It reaps huge profits - 18.5% of 2001 revenues - almost four times that of other Fortune 500 companies and far in excess of the next most profitable industry, Commercial banks (at 13.5% of 2001 revenues) - while being heavily subsidized by taxpayers through research funded by National Institutes of Health (NIH), government-granted patents and huge tax breaks. What is the extent of this control?

Drug pricing: Initial prices are too high and arbitrary and are increasing six times faster than general medical inflation. Long patents, legislated by the government, provide virtual monopolies on many drugs so that competition is no longer over price but market niche. And as if 20 years is not enough, brand-name companies are using elaborate legal procedures to extend patent protection beyond that. Holding up a generic drug by 6 months may cost a drug company several million dollars in legal fees. But that 6 month delay may yield several hundred million dollars in additional sales. The industry's justification for the high cost of drugs is the huge Research and Development costs required to bring a drug to market. However, a recent report by Public Citizen has revealed that the often quoted number of US\$500,000,000 is misleading. The actual after-tax cost for a new drug (which includes failures) has been calculated at closer to US\$100,000,000. The industry also lobbies our politicians to acquire patent extensions and advantageous policies for regulations and taxation. In the U.S. the drug industry spends \$70,000 per year to lobby each US senator and representative, and another \$7,000 per individual on campaign donations.

Research: Drug company-sponsored studies emphasis positive results, while minimizing or suppressing negative outcomes. They exaggerate the benefits of new, high-cost drugs over older, cheaper agents and minimize criticism of the safety or efficacy of their drugs. Cost-benefit analyses are heavily biased in favour of the sponsored drug. The influence of big pharma in medicine is so vast, the editors of the major medical journals such as New England Journal of Medicine and The Lancet have recently agreed to stricter rules on reporting sponsorship and conflicts of interest. A recent study in JAMA on the interactions between authors of clinical practice guidelines and the pharmaceutical industry found serious omissions in declarations of conflicts of interest. Almost 90% of authors received research funding from or acted as consultants for a drug company. More than half had financial relationships with companies whose drugs were being reviewed in the guideline.

Medical education: The drug companies provide a substantial proportion of the several billion dollars spent on medical education annually and use that support as a marketing tool. The "education" provided usually consists of skyboxes at hockey games, rounds of golf, dinners, educational vacations at luxury resorts and knickknacks of all description. Social scientists agree that the prevailing purpose of these gifts is to establish the identity of the donor in the mind of the recipient and to oblige the recipient to reciprocate. The acceptance of even small gifts is known to affect clinical judgement and heighten the perception (as well as the reality) of a conflict of interest. It is no surprise that industry-sponsored education is slanted in favour of the sponsored product and that physicians attending the sessions later prescribe these products more often than competing drugs.

Physician prescribing patterns and consumer demand: The marketing budgets of the large drug companies represent about 40% of revenues, dwarfing their research and development budgets. Canadian drug companies spend a billion dollars a year trying to influence doctors and governments. In addition to the free pens, dinners, coffee cups and trips, physicians are provided with free drug samples to hook patients on the latest, high-cost, me-too drug - physicians essentially become marketers for the drug company. The government is also coming under mounting pressure to allow DTCA from so-called "patient advocacy groups" who receive significant funding from drug companies.

The end result of this insidious manipulation by big pharma is increased use of and expenditures on drugs. And that is precisely the goal of the drug industry. But is that what the general public wants or needs? Despite the claim that DTCA is only providing what the consumer wants, recent evidence shows

otherwise. The UK Consumer's Association recently published a survey showing that the general public was deeply suspicious of industry advertising directly to patients. Of the 1818 people surveyed, only a quarter felt that drug companies could be trusted to provide unbiased and comprehensive information about drug therapy. More than half believed that the companies would try to convince people they had a non-existent illness. The drug companies are setting an agenda that advances their over-riding objective - to sell drugs, maximize profits and increase the value of their shareholders stock. I am concerned that the goals of health care are in jeopardy of becoming subsidiary to those of the pharmaceutical industry.

Strong action is needed to combat the influence of big pharma. It is the responsibility of the federal government to resist the pressure from the drug industry, and the private broadcasters, and shield the Canadian public from the profit-oriented targeting of consumers. This includes maintaining the current advertising restrictions in Canada. In addition, we (pharmacists, physicians and other health care professionals) have a responsibility to counter the heavy hand of pharmaceutical industry marketing by educating the consumer to reduce demand for the latest drug or technological intervention when there is no additional benefit. We must provide consumers with feedback that forces them to compare value against the cost.

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Evidence Based Snapshots

The Journal of Informed Pharmacotherapy 2002;10:150

Losartan versus Atenolol for Hypertension (LIFE): Overall Results and Diabetic Patient Subset

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Reviewer's profession/specialty: Associate Editor, Journal of Informed Pharmacotherapy

Original Citation

Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H; The LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. Lancet 2002;359:995-1003 [PubMed Citation](#)

Lindholm LH, Ibsen H, Dahlof B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristiansson K, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wedel H, Aurup P, Edelman J, Snapinn S; The LIFE Study Group. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. Lancet 2002;359:1004-10 [PubMed Citation](#)

Overall Study Question

These investigators examined the long term (4.8 years) benefits of treating hypertension with either losartan or atenolol.

Patients

9,193 (1195) patients mean age 67, 54% women, 25% (35%) history of vascular disease. Numbers in brackets are the the subset of patients who were diabetic at entry into the trial.

Treatment

Losartan 50-100 mg PO daily or atenolol 50-100 mg PO daily. Approximately 25% required additional drugs

Duration

4.8 years.

Results

	CV mortality, MI, stroke (%)			All deaths			MI's (%)			Stokes (%)			CV Mortality (%)		
	T	D	ND	T	D	ND	T	D	ND	T	D	ND	T	D	ND
Losartan	11	18	10	8	11	8	4	7	4	5	9	5	4	6	4
Atenolol	13	23	11	9	17	8	4	8	3	7	11	6	5	10	4
Relative Risk Reduction	15	22	Stats not done	NSS	35	Stats not done	NSS	Stats not done	29	NSS	Stats not done	NSS	Stats not done	NSS	Stats not done
Absolute Risk Reduction	2	5			6										
NNT/NNH over 4.8 years	50	20			17										

T= total, D = diabetic, ND = nondiabetic, NSS = not statistically significant

Systolic blood pressure was lowered by 1.1 mmHg more in the losartan group compared to the atenolol group.

How does this study contribute to the drug therapy of hypertension?

This study shows that losartan decreases the chance of cardiovascular events and deaths by more (2% and 6% respectively) than atenolol in patients with hypertension. The benefit was greater in diabetic patients than in patients without diabetes. Unfortunately, thiazide diuretics, the drugs of choice for hypertension were not used as a comparison in this trial.

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Evidence Based Snapshots

The Journal of Informed Pharmacotherapy 2002;10:151.

Symptom-Triggered vs. Fixed-Schedule Doses of Benzodiazepine for Alcohol Withdrawal

Reviewer: James McCormack, B.Sc. (Pharm), Pharm. D.
Reviewer's email address: jmcorma@interchange.ubc.ca
Reviewer's profession/specialty: Associate Editor, Journal of Informed Pharmacotherapy

Original Citation

Daeppen JB, Gache P, Landry U, Sekera E, Schweizer V, Gloor S, Yersin B. Symptom-triggered vs fixed-schedule doses of benzodiazepine for alcohol withdrawal: a randomized treatment trial. Arch Intern Med 2002;162:1093-4 [PubMed citation](#)

Overall Study Question

These investigators evaluated the benefit of using a symptom-triggered versus fixed-schedule doses of benzodiazepines for the prevention of alcohol withdrawal.

Patients

117 patients with alcohol dependence who were entering an alcohol dependence program. Their average age was 47 and 77% were male.

Treatment

Patients were randomized to a fixed schedule of oxazepam 30 mg Q6H for 4 doses followed by 15 mg PO Q6H for 8 doses or a symptom triggered dose (Clinical Institute Withdrawal Assessment for Alcohol scale*) which included a placebo given in a similar regimen as the fixed schedule group plus doses (15-30 mg) of oxazepam as needed based on an alcohol withdrawal scale.

* patients with scores between 8 and 15 received 15 mg of oxazepam, and those with a score higher than 15 received 30 mg of oxazepam

Duration

4 days.

Results

	Patients who received oxazepam (%)	Average total dose of oxazepam (mg)	As needed oxazepam (mg)	Total # of seizures	Hallucinations, DT's	QOL, well being
Fixed schedule (n=61)	100	231	7	0	0	NSS
Symptom based (n=56)	39	38	38	1	0	

How does this study contribute to the use of benzodiazepines in the prevention of alcohol withdrawal?

This study shows that treatment of patients who are at risk for alcohol withdrawal do as well on a symptom-triggered regimen of oxazepam as on a fixed-dose schedule. The total amount of oxazepam used is lower in the symptom-triggered group.

Evidence Based Snapshots

The Journal of Informed Pharmacotherapy 2002;10:152.

The Effect of a Proton Pump Inhibitor on the Development of Ulcer Complication Recurrences in Patients taking 100 mg ASA Daily

Reviewer: James McCormack, B.Sc. (Pharm), Pharm. D.

Reviewer's email address: jmccorma@interchange.ubc.ca

Reviewer's profession/specialty: Associate Editor, Journal of Informed Pharmacotherapy

Original Citation

Lai KC, Lam SK, Chu KM, Wong BCY, Hui WM, Hu WHC, Lau GKK, Wong WM, Yuen MF, Chan AOO, Lai CL, Wong J. Lansoprazole for the Prevention of Recurrences of Ulcer Complications from Long-Term Low-Dose Aspirin Use. N Engl J Med 2002;346:2033-8 PubMed Citation

Overall Study Question

These investigators looked to see if lansoprazole [corrected text] administration could decrease the chance of gastrointestinal toxicity from low dose (100 mg) ASA in patients who had previously developed gastrointestinal toxicity on 325 mg of ASA.

Patients

123 patients with a previous history of bleeding or gastric outlet obstruction due to gastroduodenal ulcer while receiving 325 mg of ASA daily. Their average age was 70, approximately 72% were male, and all had proven H. pylori infection.

Treatment

All patients received one-week of anti-helicobacter treatment. After that time patients were randomized to receive either placebo or lansoprazole 30 mg PO daily. The study was stopped when an interim analysis revealed a significant treatment effect, according to prespecified stopping rules.

Duration

The median duration of follow up was 12 months.

Results

	Bleeding, perforation or obstruction (%)
Lansoprazole	2 [corrected text]
Placebo	15 [corrected text]
Relative Risk Reduction	87
Absolute Risk Reduction	13
NNT/NNH over 12 mos	8

Other results

Side effects were not reported

How does this study contribute to the drug therapy of prevention of gastrointestinal toxicity from ASA used for cardiovascular prophylaxis?

This study demonstrates that a proton pump inhibitor decreases the chance of clinically important gastrointestinal toxicity from ASA in patients who had already experienced gastrointestinal toxicity on ASA.

Corrected Text

Originally published as "omeprazole". Corrected to "lansoprazole" on 9AUG02.

In the results table the percentages for bleeding, perforation or obstruction in the lansoprazole and placebo groups were originally published in reverse. On 9AUG02, the values were corrected as above.

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Evidence Based Snapshots

The Journal of Informed Pharmacotherapy 2002;10:154

Risks and Benefits of Estrogen plus Progestin in Healthy Postmenopausal Women (Women's Health Initiative)

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Reviewer's profession/specialty: Associate Editor, Journal of Informed Pharmacotherapy

Original Citation

Writing Group for the Women's Health Initiative. Risks and Benefits of estrogen plus progestin in healthy postmenopausal women - Principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-3 [Fulltext Article](#)

Overall Study Question

This study is the first randomized controlled trial to look at the long term benefit and harm of hormone replacement in healthy postmenopausal women.

Patients

16,608 women, mean age 63. Four percent were being treated for diabetes, 36% were being treated for hypertension, 13% were being treated for elevated cholesterol and 11% were smokers.

Treatment

Women received either conjugated equine estrogen 0.625 mg PO daily PLUS medroxyprogesterone 2.5 mg PO daily or placebo.

Duration

5.2 years - the study was supposed to be 8.5 years in length but was stopped early due to health risks exceeding benefits.

Results

	CHD (%)	Stroke (%)	DVT (%)	PE (%)	Total CVD (%)	Breast Cancer (%)	Colorectal cancer (%)	Hip fractures (%)	All fractures (%)	Deaths (%)	Global Index (%)
Estrogen/progestin	1.9	1.5	1.4	0.8	8.2	2.0	0.5	0.5	7.6	2.7	8.8
Placebo	1.5	1.0	0.6	0.4	6.7	1.5	0.8	0.8	9.7	2.7	7.7
Relative Risk Reduction/increase	27	50	133	100	22	33	38	38	22	NSS	14
Absolute Risk Reduction/increase	0.4	0.5	0.8	0.4	1.5	0.5	0.3	0.3	2.1		1.1
NNT/NNH over 5.2 years	250	200	125	250	67	200	333 [corrected text]	333	48		91

Results are statistically significant using at least nominal 95% CIs - NSS = not statistically significant

CHD = coronary heart disease, DVT = deep vein thrombosis, PE = pulmonary embolism, CVD = cardiovascular

Global index - represents the first event for each participant from among the following types - CHD, stroke, pulmonary embolism, breast cancer, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes

How does this study contribute to the drug therapy of hormone replacement?

This study suggests that other than for symptom control, the harms of long-term hormone replacement outweigh the benefits.

Corrected Text

Originally published as "33". Corrected to "333" on 9AUG02.

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Evidence Based Snapshots

The Journal of Informed Pharmacotherapy 2002;10:155

Heart Protection Study - Use of Simvastatin in "High Risk" Individuals

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Reviewer's profession/specialty: Associate Editor, Journal of Informed Pharmacotherapy

Original Citation

Health Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,356 high-risk individuals: a randomized placebo-controlled trial. Lancet 2002;360:7-22 [PubMed Citation](#)

Overall Study Question

These investigators evaluated the benefit of treating "high risk" patients with simvastatin.

Patients

20,536 "high risk" patients (76% males, 29% at least 70 years of age). High risk was defined as patients with previous MI (41%) or CHD (24%), occlusive disease of non-coronary arteries (22%), diabetes (20%), treated hypertension (41%), PLUS a total cholesterol greater than 3.5 mmol/L. Patients could have a combination of these risk factors.

Treatment

Simvastatin 40 mg PO daily or placebo.

Duration

5 years.

Results

	All deaths (%)	Any major vascular event (%)	Coronary events (%)	Strokes (%)

Simvastatin	12.9	19.8	8.7	4.3
Placebo	14.7	25.2	11.8	5.7
Relative Risk Reduction	12	21	26	25
Absolute Risk Reduction	1.8	5.4	3.1	1.4
NNT/NNH over 5 years	56	19	32	71

Other results

Total cholesterol was lowered by 1.0 mmol/L on average.

Relative reductions in the primary endpoint were similar for patients regardless of sex, age, total/LDL/HDL levels, or whether or not they had had a previous MI, other CHD, CVD, PVD, or diabetes.

No differences were detected between groups for elevated liver enzymes, cancers, myopathies, fractures, or neuropsychiatric disorders.

How does this study contribute to the drug therapy of cardiovascular protection?

This study shows that simvastatin given to "high risk" patients, regardless of age or sex, or baseline cholesterol levels lowers the chance of cardiovascular events.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2002;10:200.

Effects of Clopidogrel Plus Aspirin in Acute Coronary Syndromes Without ST-segment Elevation: A CURE for What Ails You?

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Reviewer's profession/specialty: Pharmacy, Cardiology, Cardiovascular surgery

Original Citation

Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502.

PubMed Citation

Overall Study Question

Antithrombotic and antiplatelet agents have been major pharmacological advances in reducing the risk of death from cardiovascular causes, myocardial infarction, and recurrent ischemia in non-ST-elevation acute coronary syndromes (NSTEMI). While the use of aspirin (1), unfractionated heparin (2)/low-molecular weight heparin (LMWH)(3) and intravenous glycoprotein IIb/IIIa receptor inhibitors (GP IIb/IIIa inhibitors)(4,5) have been shown to reduce the incidence of early cardiovascular events in specific patients with NSTEMI, a high rate of major vascular events in this patient population still persists. Although aspirin is recommended to be continued indefinitely, there is no convincing evidence to support the use of LMWH or GP IIb/IIIa antagonist beyond the acute period. (6) It has been suggested that the thienopyridine antiplatelet clopidogrel may have added benefit when given with aspirin in reducing long-term risk of ischemic events.

The CURE trial was an international, multi-centre, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of clopidogrel, plus aspirin with those of aspirin alone in non-ST-elevation acute coronary syndromes.

Consenting patients were enrolled if they had been hospitalized within 24 hours after the onset of symptoms that were consistent with ischemia. Ischemia was defined as unstable angina or acute myocardial infarction (MI) without ST-segment elevation greater than 1 mm and had either electrocardiographic (ECG) changes or an elevation in serum cardiac enzymes or markers. Exclusion criteria included a contraindication to antithrombotic or antiplatelet therapy, the use of oral anticoagulants, a high risk for bleeding or severe heart failure, a coronary revascularization procedure

within the previous three months, or receipt of a intravenous GP IIb/IIIa inhibitors within the previous three days.

Patients were immediately randomized to receive a 300 mg loading dose of clopidogrel (or matching placebo) followed by 75 mg of clopidogrel (or matching placebo) for 3 to 12 months. At the discretion of the physician in charge, patients concurrently received aspirin in a dose range of 75 mg to 325 mg daily. Follow-up assessments occurred at discharge from hospital, at one and three months, and then every three months until the end of the study.

The first primary outcome of this study was the composite of death from cardiovascular causes, nonfatal MI, or stroke. The second primary outcome was the composite of the first primary outcome plus refractory ischemia. The secondary outcomes for this study were severe ischemia, heart failure, the need for revascularization and bleeding complications.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

After informed consent was obtained, patients were randomly assigned to either the clopidogrel group or the placebo group by a central, 24-hour, computerized randomization service from the Canadian Cardiovascular Collaboration Project Office. Permuted-block randomization, stratified according to clinical centre was used.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Patients were recruited between December 1998 and September 2000 at 482 centers in 28 countries. A total of 12,562 patients were enrolled; 6,259 received clopidogrel and 6,303 received placebo. All analyses were based on the intention-to-treat principle. Six patients in the clopidogrel group and 7 patients in the placebo group were lost to follow-up.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

This was a double-blinded study. Two formal interim assessments were performed by a blinded independent data and safety monitoring board when approximately one-third and two-thirds of the expected events had occurred.

4. Were the groups similar at the start of the trial?

The baseline demographics and characteristics of the patients in both groups were similar including admitting diagnosis, medical history, time from onset of pain to randomization, ECG abnormalities and cardiovascular medication history. Unfortunately, the authors provided no information regarding the rates of significant family history of coronary artery disease or

cholesterol profiles for the patient groups. This would have been useful to further define patient baseline characteristics. Considering the sample size and study design, it is reasonable to assume that these factors would likely be balanced across groups.

5. Aside from the experimental intervention, were the groups treated equally?

Subsequent to randomization there were no restrictions on the use of any therapy or interventions. More invasive management strategies were discouraged, however, and only 7.2% in the placebo group and 5.9% in the clopidogrel group received GP IIb/IIIa inhibitors. If the clinicians determined that angiography and revascularization were needed or that a thienopyridine derivative was indicated, the study medication could be stopped or open-label clopidogrel or ticlopidine could be used.

Overall, 43.7% of patients underwent angiography, 16.5% underwent coronary artery bypass graft (CABG) and 21.2% underwent percutaneous transluminal coronary angioplasty (PTCA). A similar proportion of patients in both arms underwent revascularization (36.9% in the placebo group vs. 36% in the clopidogrel group). In both groups the study medication was recommended to be temporarily stopped for more than 5 days if patients underwent PTCA or CABG, and the majority of patients with PTCA received a thienopyridine-type agent for about two to four weeks after.

What were the Results?

1. How large was the treatment effect?

Patients were treated for 3 to 12 months (mean duration of treatment 9 months). The first primary outcome (death from cardiovascular causes, nonfatal MI, or stroke) occurred in 9.3% of the clopidogrel group and 11.4% of the placebo group ($p < 0.001$, ARR = 2.1%, RRR = 18.4%, NNT = 48). There was no significant reduction in cardiovascular death or stroke, only nonfatal myocardial infarction was reduced significantly from 6.7% to 5.2% ($p < 0.001$). The second primary outcome (first primary outcome or refractory ischemia) occurred in 16.5% of the clopidogrel group and 18.8% of the placebo group ($p < 0.001$, ARR = 2.3%, RRR = 12.2%, NNT = 43). The rate of other in-hospital outcomes (severe ischemia, recurrent angina, need for coronary revascularization) also tended to be lower in the clopidogrel group. The benefits were consistent among various subgroup analyses including both high-risk and low-risk features, in those receiving different doses of aspirin, and various proven therapies such as angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, lipid-lowering drugs prior to study enrollment. Further analysis indicated that the benefit of clopidogrel was apparent within a few hours after randomization and significantly lower in the clopidogrel group by 24 hours.

Clopidogrel was associated with a significant increase in major and minor bleeding. Major bleeding occurred in 3.7% in the clopidogrel group and 2.7% in the placebo group ($p = 0.001$, ARI = 1.0%, RRI = 38%, NNH = 100). Minor bleeding episodes were significantly increased in the clopidogrel group at 5.1% compared with the placebo group at 2.4% ($p < 0.001$, ARI = 2.7%, RRI = 113%, NNH = 37). There was no significant increase in the risk of

life-threatening bleeding which occurred in 2.2% in the clopidogrel group and 1.8% in the placebo group ($p = 0.13$, ARI = 0.4%, RRI = 22%, NNH = 250). The excess major bleeding episodes were gastrointestinal hemorrhages and bleeding at the sites of arterial punctures. The number of patients who required transfusions of greater than or equal to 2 units of blood was 2.8% in the clopidogrel group and 2.2% in the placebo group ($p = 0.02$). Overall, there was no significant increase of major bleeding episodes after CABG (8.3% in the clopidogrel group vs. 6.6% in the placebo group)(7). However there was a trend towards a higher bleeding rate in those receiving clopidogrel within five days of surgery, with major bleeding rates of 9.6% in clopidogrel group and 6.3% in placebo group ($p = 0.06$, RR = 1.53). The incidence of thrombocytopenia or neutropenia was similar in both groups.

A total of 46.2% of patients in the clopidogrel group temporarily stopped the study medication (for more than five days) and 45.4% of patients in the placebo group. The study medication was permanently discontinued in 21.1% of the clopidogrel group and 18.8% of the placebo group. The use of other medications was similar in both groups.

2. How precise was the estimate of the treatment effect?

The relative risk 95% confidence intervals for the first primary outcome was 0.72 to 0.90 and for the second primary outcome was 0.70 to 0.94. These confidence intervals are narrow and do not cross one (i.e. the point of unity) supporting the statistically significant result.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

This international study involving 28 countries had a large representation of patients from Europe, Canada and U.S. The inclusion and exclusion criteria are consistent with other NSTEACS trials and would suggest general applicability to patients in centres that do not routinely conduct early invasive interventions as those who had received early coronary intervention or GP IIb/IIIa antagonists were excluded from the study.

Although patients were excluded if they had received coronary revascularization in the previous three months, once a patient was randomized to a treatment group, there were no restrictions on the use of any therapy or interventions that was believed to be necessary. In patients who underwent PTCA or CABG, the study medication was recommended to be temporarily interrupted for more than five days and the majority of the patients who underwent PTCA received open-label thienopyridine antiplatelet agent for two to four weeks. The study medication was restarted after a median of 11 days in the patients who underwent CABG.

2. Were all clinically important outcomes considered?

All important outcomes were considered and clearly defined. It is interesting to note

that the CURE study involved two primary outcomes (see above). It is not expected that this would have affected the significance of the study results as the authors described appropriate statistical adjustments.

3. Are the likely treatment benefits worth the potential harms and costs?

Clopidogrel in addition to aspirin significantly decreased the incidence of the first and second primary outcomes. However this occurred at the expense of an increase in major and minor bleeding, although there was no increase in the risk of life-threatening bleeding. (7)

Finally, it is important to consider whether the benefit of therapy outweighs the financial cost. Clopidogrel costs approximately \$3 per day in the U.S. and \$2.90 per day in Canada (for a total of \$783 CDN for 9 months excluding dispensing fee). Although this will not be an issue for in-hospital costs, it may be a barrier to long-term treatment for elderly patients (who are the majority of ACS patients) on government assistance plans that do not readily cover the cost of clopidogrel outside the hospital. A full cost-effectiveness economic analysis of the study is expected to be presented later.

Commentary

Although there are now many treatments for the acute management of non-ST-elevation acute coronary syndrome, only aspirin is used long-term. (6) The benefit of a short-term combination of aspirin plus a thienopyridine derivative in lowering the rates of myocardial infarction is established in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) with stenting. (8) The CURE trial demonstrates the benefit of adding clopidogrel to the treatment regimens for patients with NSTEMI who are receiving aspirin and other medications but with an increased risk for bleeding.

The baseline characteristics of the patients in the CURE trial are consistent with the patient population seen in other NSTEMI studies. It can be argued that the patients in CURE are of a moderate to high-risk category as a large number of patients (93.8%) presented with ECG positive changes at entry. This is consistent with the patient population seen in the PURSUIT and PRISM-PLUS trials where greater than 99% and 94% respectively had positive ECG changes while only over 55% of the patients in ESSENCE had reported ECG changes at baseline. (3-5) However, there were more patients who had positive enzymes and ST depression in the GP IIb/IIIa inhibitor trials than either the ESSENCE or CURE trials (enzymes: 45% (4,5) vs. 21% (3) and 25% (CURE) ; ST depression: 49-58% (4,5) vs. 24% (3) & 42% (CURE)). This would suggest that there are some similarities in the level of risk of patients in the CURE trial and the GP IIb/IIIa inhibitor trials and that the CURE patients might also have been considered candidates for GP IIb/IIIa inhibitor therapy +/- invasive interventions. However, the event rates in the placebo group in the CURE trial suggest an intermediate risk population when compared with other NSTEMI trials. In CURE, 12.1% of the placebo group experienced death or MI at 9 months compared to 13.5% in the ESSENCE study at 1 year and 15.7% in the PURSUIT4 study at 30 days and 15.4% in the PRISM-PLUS5 study at 6 months.

It is important to note that the bleeding definitions used in the CURE trial were different from the standard GUSTO and TIMI bleeding scales more commonly used in other NSTEMI trials. The bleeding

definitions used in the CURE trial were more stringent than either GUSTO or TIMI bleeding scales and resulted in higher bleeding rates. When analyzed by the GUSTO and TIMI scales, no differences between groups was found.

The CURE trial excluded patients who had received a GP IIb/IIIa inhibitor within the previous 3 days or those who had received a revascularization within the previous 3 months. Therefore, the role of clopidogrel is still unknown in this patient population.

With respect to risk versus benefit, the results from the CURE trial indicate that treating 1000 patients for 9 months prevents 20 events (cardiovascular death, nonfatal MI, or stroke) at a cost of 10 major bleeds. The risk of major bleeding in CURE is comparable to the GP IIb/IIIa inhibitor trials, but higher than the major bleeding rates in the ESSENCE study with enoxaparin. It is difficult to make definitive comments regarding the risk versus benefit of clopidogrel compared with current antithrombotic and antiplatelet agents used in NSTEMI management due to the different primary endpoints that are evaluated in each study. This fact emphasizes the importance of early risk-stratification of NSTEMI patients to target therapy at the appropriate level to maximize benefit.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2002;10:201.

Tissue Plasminogen Activator During Cardiac Arrest: No Better Than Placebo?

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Reviewer's profession/specialty: Pharmacist / Emergency Medicine

Original Citation

Abu-Laban RB, Christieson JM, Innes GD, van Beek CA, Wanger KP, McKnight RD, MacPhail IA, et al. Tissue plasminogen activator in cardiac arrest with pulseless electrical activity. N Engl J Med 2002;346:1552-8. [PubMed Citation](#)

Overall Study Question

This study was conducted to determine the efficacy of administration of tissue plasminogen activator (t-PA) during cardiopulmonary resuscitation (CPR) in adults with undifferentiated pulseless electrical activity (PEA) not responsive to initial therapy. Adults (>16 years of age) who had more than 1 minute of PEA and were unresponsive to initial therapy (endotracheal intubation and ventilation with 100% oxygen, 500 mL of normal saline and 1 mg of intravenous (IV) epinephrine) outside the hospital were eligible for the study. The primary endpoint was survival to hospital discharge. The secondary endpoints included return of spontaneous circulation (ROSC), length of hospital stay, hemorrhage and neurological outcome.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Patients were randomized to receive either tPA 100 mg IV over 15 minutes or matching placebo.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. 233 patients met inclusion criteria and were randomized (117 tPA and 116 placebo). All patients were included in the final analysis.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. The study was double-blinded. The appearance of the tPA and placebo before and after reconstitution was indistinguishable.

4. Were the groups similar at the start of the trial?

Yes. The baseline characteristics of the tPA and placebo groups were similar.

5. Aside from the experimental intervention, were the groups treated equally?

Yes. There were no differences in the further treatment of patients assigned to tPA or placebo. Once infusion of the study drug commenced, the infusion was completed regardless of whether a pulse developed. Resuscitative efforts were continued for a minimum of 15 minutes after the infusion was completed, and further treatment was at the discretion of the CPR leader.

What were the Results?

1. How large was the treatment effect?

The primary endpoint, survival to hospital discharge, occurred in 1(0.9%) patient treated with tPA compared to none (0%) who received placebo. The absolute difference in survival between the tPA group and placebo group was 0.9% (95% confidence interval [CI] -2.6 to 4.3, p=ns).

The secondary endpoint of ROSC occurred in 21.4% of patients in the tPA group and 23.3% of patients in the placebo group (p=ns).

2. How precise was the estimate of the treatment effect?

The 95% CI for the primary endpoint of survival to hospital discharge included zero indicating a non-statistically significance result (0.9%, 95% CI -2.6-4.3, p=ns).

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. The use of tPA in a patient population consisting of undifferentiated PEA does not appear to be beneficial in improving overall survival.

2. Were all clinically important outcomes considered?

Yes. In cardiac arrest research the ultimate endpoint is overall survival which was the primary endpoint in this trial.

3. Are the likely treatment benefits worth the potential harms and costs?

No.

Commentary

There are several case series which describe neurologically normal survival in patients with prolonged cardiac arrest following the administration of fibrinolytics. (1,2) However, a majority of these reports represent select patient populations in which the patients were known or likely to be experiencing cardiac arrest secondary to a thromboembolic event such as myocardial infarction and massive pulmonary embolism. In a non-randomized, prospective study using historical controls found that treatment with tPA significantly increased the rate of ROSC and hospital admission. (3) In a non-randomized, retrospective, case-control study, tPA was found to improve rates of ROSC, 24-hour survival and survival to hospital discharge. (4)

This is the first trial which involved the prospective randomization of a population of undifferentiated cardiac arrest patients to receive tPA or placebo and found no evidence that tPA during CPR improved the likelihood of either survival or ROSC. It is difficult to determine the reason why this study had such a low survival rate, although this may be explained by the undifferentiated patient population enrolled. The fact that there appears to be no benefit to patients in cardiac arrest with undifferentiated PEA leads the clinician to conclude that this strategy is not advantageous. However, as the authors clearly state, the results of this trial cannot be generalized to a highly selective population of patients with cardiac arrest with a known or suspected pulmonary embolism or myocardial infarction meeting criteria for the administration of fibrinolytics.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2002;10:202.

Can the Eradication of Helicobacter pylori Reduce the Risk of Peptic Ulcer Disease in Patients Starting NSAIDS?

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Reviewer's profession/specialty: Clinical pharmacists; Internal Medicine and Neurosciences

Original Citation

Chan FKL, To KF, Wu JCY, Yung MY, Leung WK, Kwok T, et al. Eradication of Helicobacter pylori and risk of peptic ulcers in patients starting long-term treatment with non-steroidal anti-inflammatory drugs: a randomised trial. Lancet 2002;359:9-13 [PubMed Citation](#)

Overall Study Question

To determine if eradication of Helicobacter pylori will reduce the risk of ulcers among patients positive for H pylori who have dyspepsia or a history of ulcer, and are about to start long-term non-steroidal anti-inflammatory drug (NSAID) treatment. All patients were NSAID naïve. The study sample included 100 arthritis patients, including 33 males and 67 females, with a mean age of 63 years. Sixteen patients had a history of ulcer, 60 patients had coexisting illness (cerebrovascular accident, ischemic heart disease, heart failure, chronic obstructive airway disease and chronic liver disease), and 17 used low dose ASA concurrently with NSAIDs.

The primary outcome variable was endoscopically proven gastric or duodenal ulcers. The secondary outcome was complicated ulcers - symptomatic and bleeding ulcers. The study intervention was triple therapy with oral omeprazole 20 mg, amoxicillin 1000 mg, and clarithromycin 500 mg each given twice daily for 1 week. The control group received oral omeprazole 20 mg, and placebo.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. One hundred of the 102 randomized patients (98%) were accounted for in the final analysis. The 2 patients not included in the final analysis withdrew from the placebo group prior to receiving any medication.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. The study investigators, study nurse, endoscopists, pathologists and patients were all blinded. Placebo medications were identical in appearance to study medications.

4. Were the groups similar at the start of the trial?

Yes. The two groups were similar for most of the reported baseline characteristics. The only potentially important difference was that the placebo group contained more smokers (10% vs. 18%).

5. Aside from the experimental intervention, were the groups treated equally?

Yes. Both groups were treated identically.

What were the Results?

1. How large was the treatment effect?

The 6-month probability of ulcers was 12.1% in the treatment group and 34.4% in the placebo group (log rank test, $p=0.0085$). The 6-month probability of complicated ulcers was 4.2% in the treatment group and 27.1% in the control group (log rank test, $p=0.0026$).

In the Cox's proportional hazard model only, assignment to the placebo group was significantly associated with an increased risk of ulcers (hazard ratio 3.3 [95% CI 1.2-7.9]) and complicated ulcers (6.5 [95% CI 1.4-29.5]). Among patients with previous ulcer disease 1 of 7 in the treatment group and 5 of 9 in the placebo group had recurrent ulcers within 6 months ($p=0.15$). Among those who concurrently used low dose ASA, 1 of 9 in the treatment group and 2 of 8 in the placebo group developed ulcers within 6 months ($p=0.58$).

Finally, 43% of patients in the treatment group and 35% in the placebo group reported gastrointestinal upset during the first week of treatment ($p=0.42$).

2. How precise was the estimate of the treatment effect?

The 6-month probability of ulcers was 12.1% (95% CI 3.1-21.1) in the treatment group and

34.4% (95% CI 21.1-47.7) in the placebo group. Our calculation of the 95% confidence intervals for the ARR of 22.3% is 7%-38% (NNT 3-14).

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. This trial indicates that NSAID naive arthritis patients who are *H pylori* positive and have a history of dyspepsia or endoscopically proven peptic ulcer requiring long term regular NSAID treatment receive benefit from *H pylori* eradication begun concomitantly with NSAID treatment.

2. Were all clinically important outcomes considered?

The authors considered the probability of ulcers and complicated ulcers (bleeding or symptomatic) at 6 months. The Cox's proportional hazard model was used to adjust for possible confounding covariates including age, coexisting illness, concurrent use of low dose aspirin, and previous ulcer disease. The authors could have considered ulcer disease beyond 6 months.

3. Are the likely treatment benefits worth the potential harms and costs?

A potential benefit of *H pylori* eradication is reduced dyspeptic symptoms. This small trial demonstrated a trend towards less dyspepsia in patients who received eradication therapy, as compared to those who received placebo. A potential harm of *H pylori* eradication is GI upset. In this study however, the relative incidences of GI upset during the first week of the study were similar between the eradication and placebo groups. The approximate drug acquisition cost for the *H pylori* eradication regimen used in this trial is ~\$100-120 CAN. A decision analysis model has indicated screening and treatment of *H pylori* would be cost effective if it reduces ulcer risk by 50%. (1)

Commentary

There has been long standing controversy as to whether or not the presence of *H pylori* influences the risk of acquiring ulcers while on NSAID therapy. A recent meta-analysis has found that both *H pylori* and NSAID use are independent risk factors for developing peptic ulcer disease (PUD) and ulcer bleeding and that there is synergy in their ulcerogenic tendencies. (2)

Logically, clinicians wonder if eradication of *H pylori* will decrease the incidence of PUD and bleeding in patients on NSAIDs. This study provides evidence that in older patients naïve to NSAIDs, eradication of *H pylori* offers clinical benefit in reducing the incidence of ulcers and/or bleeding at 6 months. It also backs up the results of a previous study by these authors that addressed the same question in patients with no history of dyspepsia or ulcer. (3) These results should be interpreted with caution however, because only 16% of patients had pre-existing peptic ulcer disease, an important risk factor for future ulcer or bleeding.

Whether this data can be extrapolated to other populations is unknown. It is apparent that the results cannot be extrapolated to those already on chronic NSAID treatment, as a previous study has shown that these patients do not have reduced ulcer risk from eradication of *H pylori*. (4)

Another interesting question is whether COX-2 inhibitors are less likely to produce ulceration and bleeding in those infected with *H pylori*. The belief that COX-2 inhibitors cause less GI complications than traditional NSAIDs may tempt clinicians to advocate using a COX-2 inhibitor alone in *H pylori* infected patients, without first eradicating the *H pylori*. However, evidence suggests that COX-2 inhibitors also increase the ulcer risk of patients with *H pylori* infection. (5) Therefore, a strategy of using COX-2 without eradicating *H pylori* can not be advocated at this time.

Finally, in patients with a history of peptic ulcer disease, or even dyspepsia (which is infrequently associated with ulcer disease), is it necessary to provide continual cytoprotection (e.g. misoprostol or a proton pump inhibitor) once *H pylori* has been eradicated? The ulcer rate at 6 months in the eradication group was lower, but was still 10%. This trial does not answer that question, although based on a review of other evidence, that strategy in patients with previous ulcer disease may be reasonable. (6)

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Technology in Practice

How to Use Email and the Internet to Help You Keep Up With the Literature (Part II): PubMed and Allied Journal Club

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J Inform Pharmacother 2002;10:500.

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Introduction

This is the second installment of a multipart series aimed at helping health care professionals use technology to keep current with professional literature. Effective use of technology is needed to selectively sort through the thousands of new literature citations that become available on a weekly basis. Part I of this series outlined how journal contents can be delivered to you by email (eTOC) directly from the publisher. (1) This installment will review two additional technology-based surveillance strategies for keeping aware of professional publications. These strategies include using the PubMed database Cubby feature and a free online literature alerting service called Allied Journal Club (AJC)

Option 1. PubMed

PubMed is an Internet database developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM), located at the National Institutes of Health (NIH) in the USA. PubMed indexes and provides free access to several databases which include: MEDLINE, out-of-scope citations (e.g. articles on the geo or astro sciences), citations from MEDLINE journals that precede the date determined MEDLINE indexing process, selected life science journals that submit full text to PubMed and are qualitatively reviewed by the NLM. (2,3) PubMed databases are accessible via Entrez; a text base database search and retrieval system developed by and used at NCBI. Readers may be familiar with the MEDLINE searching capability of PubMed, there are; however, additional features that can be used to improve searching efficiency and enable users to browse journal contents and citation abstracts. "Journal browser" is a feature that allows users to view citations from specified journals and is available for any PubMed indexed journal. "PubMed Cubby" is a feature that has three major functions one of which is to enable users to store search strategies that can be executed and updated at any

time. Additional features include, LinkOut preferences, and storage of document delivery service preferences. A description of LinkOut and document delivery aspects of PubMed is available online at <http://www.ncbi.nlm.nih.gov/entrez/query/static/help/pmhelp.html#cubby>.

Using PubMed Cubby To Screen The Literature

As was outlined in [part I](#) of this series, an eTOC service can be a convenient way to screen professional journal contents. Unfortunately, not all journal publishers provide this service. Three journals which do not currently have an eTOC service include the [American Journal of Health-Systems Pharmacy \(AJHP\)](#), [Pharmacotherapy](#), and The [Lancet](#). In order to review the contents of these journals, readers can use the "[Journal Browser](#)" feature in PubMed and store the search strategy in [Cubby](#) for regular updates and review.

What follows is a step-by-step example of how to use the PubMed [Cubby](#) to keep up to date with AJHP, Pharmacotherapy, and the Lancet.

Step 1. Activate A Cubby Account

In order to save and update searches PubMed users must activate a [Cubby](#) account. A [Cubby](#) can be activated by going to the main PubMed page at <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed> and clicking on the [Cubby](#) link in the left column menu. Clicking on this link will take users to a Cubby login/registration page (Figure 1).

Figure 1. PubMed Cubby Login/Registration Page

The screenshot shows the PubMed Cubby interface. At the top, there's a navigation bar with links like 'PubMed', 'Bookshelf', 'Periodicals', 'Database', 'Statistics', 'PopSet', 'Taxonomy', and 'Cubby'. Below this is a search bar with a 'Go' button. A left sidebar contains links such as 'About Entrez', 'Entrez PubMed', 'Cubby Resources', and 'Change Password/Log Out'. The main content area has a heading 'Cubby' and a description: 'The Cubby provides you with a Stored Search feature to store and update searches. It also allows you to customize your LinkOut display to include or exclude links to providers. See [Help](#) for additional information.' Below this is a note: 'The Cubby requires that your system accept [cookies](#).' There's a section for 'Login for Registered Cubby Users:' with input fields for 'User Name:' and 'Password:', and a 'Login' button. To the right of the login fields are links: 'I Want to [Register](#) for Cubby' and 'Help! [I Forgot My Password](#)'. At the bottom, it says 'Welcome to the National Center for Human Genome Research'.

Make sure that your web browser is set to accept "cookies" and click the "I Want to Register for Cubby" link. Once you have activated a Cubby, you can use the journal browser feature to search for the contents of any PubMed indexed journal.

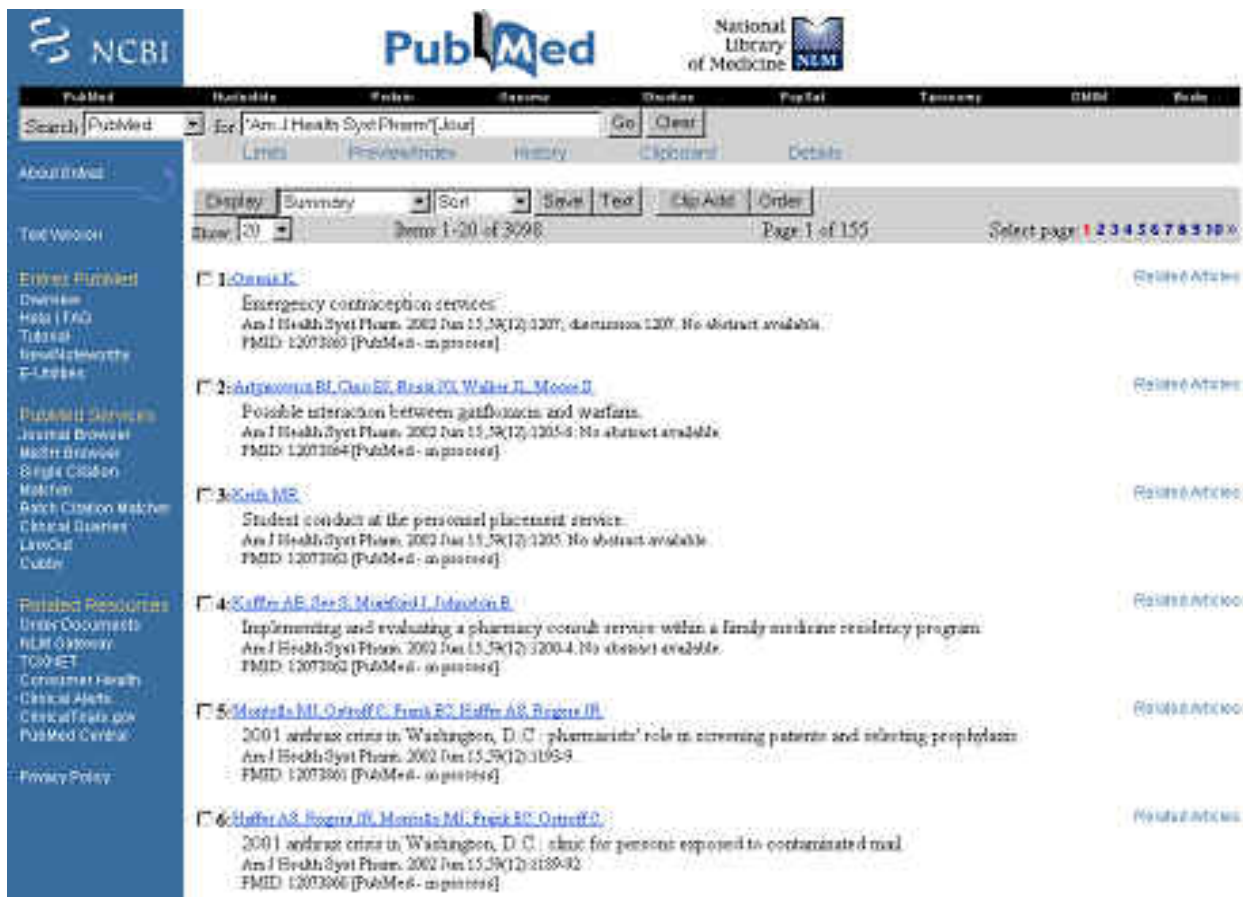
Step 2. Run a Journal Browser Search

After registering for Cubby, return to the main PubMed page by clicking on the "PubMed" link along the top horizontal border on the Cubby login/registration page. From the main page, users can activate the "Journal Browser" feature by clicking on the "Journal Browser" link in the left menu column. In order to view the contents of AJHP, type "American journal of health-system pharmacy" into the search bar. Journals titles matching the search text string will be displayed (Figure 2). Clicking on the journal MEDLINE abbreviation in the right column will display the citations from that particular journal (Figure 3).

Figure 2. PubMed Journal Browser Search



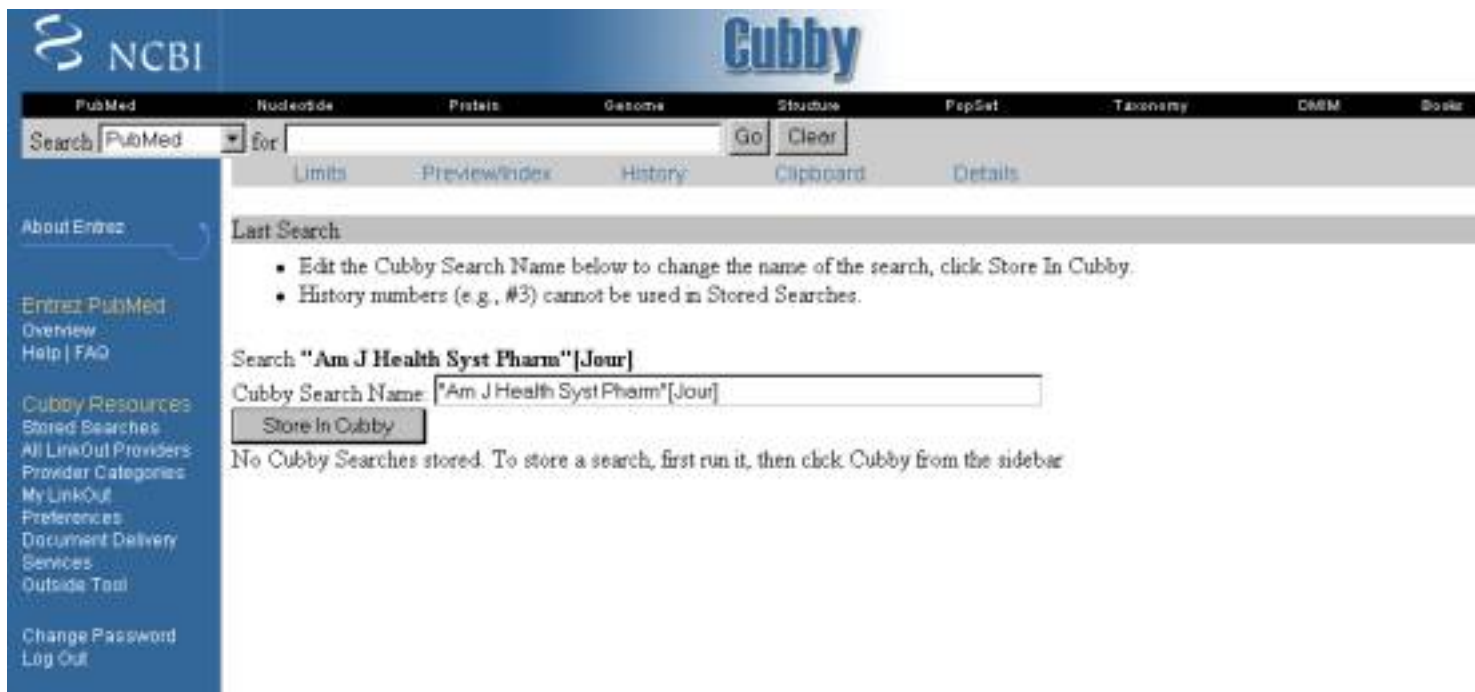
Figure 3. PubMed Journal Browser Search Citations for American Journal of Health-Systems Pharmacy



Step 3. Save The Search

Once you have searched PubMed for AJHP using the journal browser, you can save the search strategy for this journal by clicking the Cubby link on the left side bar. Cubby will display your search and you can save this search strategy by clicking the "store in Cubby" button (Figure 4).

Figure 4. Store Search in Cubby by Clicking the "Store in Cubby" Button.



Step 4. Search for Additional Journals

Return to the main Journal browser screen in PubMed and repeat the above process for additional journals that you wish to review (e.g. Pharmacotherapy and Lancet). Save these searches in Cubby as described above. These journal searches will be listed separately in the stored searches section of the Cubby (Figure 5).

Figure 5. Cumulative Stored Searches in Cubby



Step 5. Periodically Update Your Search And Review The Results

In order to keep up with new contents for selected journals, saved searches must be periodically updated. Choosing a convenient schedule (e.g. bi weekly) to do so can make this process a simple habit. In order to update the search, login to your PubMed Cubby. You will be presented with a list of your stored searches (Figure 5). Clicking on the search name will reveal information about the stored search and will present a "search" button. Clicking on the search button will simply rerun the search without update limits. In order to selectively check for new citations since your last search you can click on the checkboxes next to the name of the journal that you wish to review and then click on the "What's New for Selected" button. If new citations are available they will appear as a numeric value in an additional column (Figure 6). Click on the numeric value to review the new citations.

This PubMed Journal Browser and Cubby strategy can be used to keep up to date with the contents of any PubMed indexed journal. Users are limited to storing 100 searches per Cubby but can activate an unlimited number of Cubby accounts.

Figure 6. Updating A Saved Search Figures Indicating New Citations



Option 2: Allied Journal Club

Allied Journal Club (AJC) is a free Internet-based healthcare literature alerting service. This service is perhaps one of the simplest and most convenient ways of being alerted to the availability of new literature. AJC includes alerting options for many mainstream medical and pharmacy journals. A complete journal list for the AJC service is outlined online at <http://www.alliedjournalclub.com/journalist.shtml>.

AJC uses an automated email notification system whereby subscribers can be alerted to the availability of new contents in selected journals. The email notification provides a link to the PubMed citations for

the journal and from that point the citation titles and abstracts can be reviewed. Neither the citation titles nor abstracts are included in an AJC email alert. Rather, the subscriber must follow the link provided in the email to view the citation. An example of an AJC notification for the Lancet is provided in Figure 7.

Setting up literature alert notifications with AJC

Step 1. Go to the website AJC <http://www.alliedjournalclub.com/index.shtml>

Step 2. Click on the "sign up today link" and enter the required contact information (Figure 8)

Step 3. Scroll down the page and indicate which journals you wish to be keep track of (Figure 9)

Step 4. Check your email.

Figure 7. Allied Journal Club Email Alert For Lancet Content

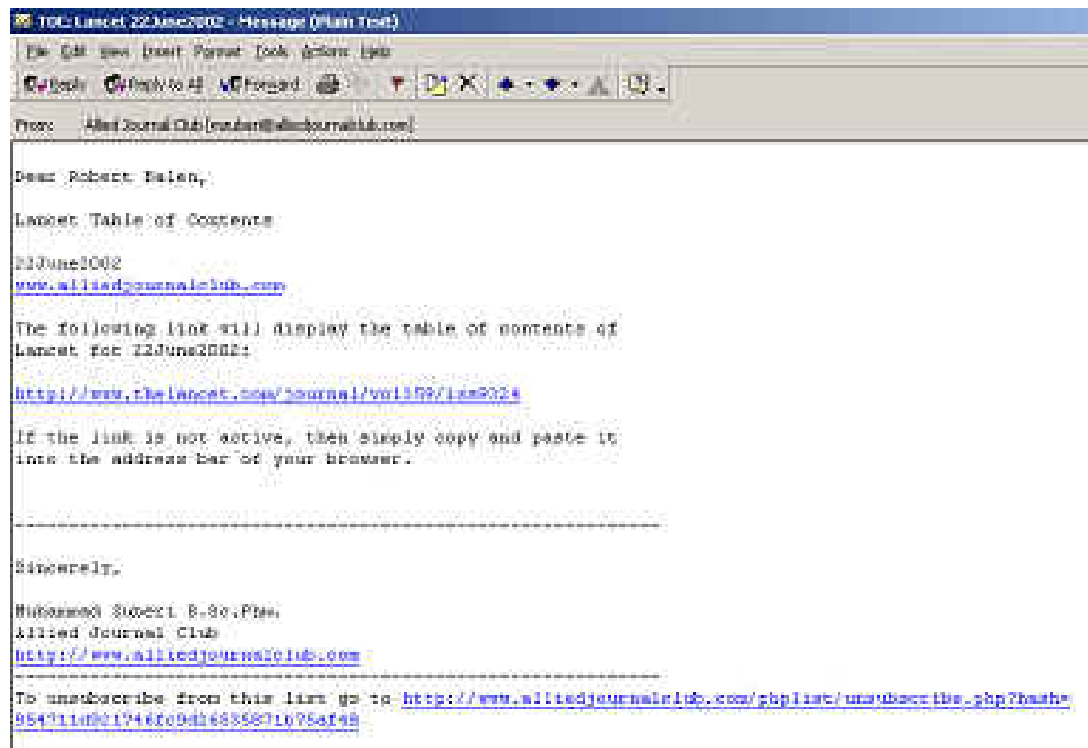


Figure 8. Allied Journal Club Sign Up Page

file:///Users/jewesson1/Desktop/JIP%20Website/Issue10/TIPS/Keeping%20up%20pt2.htm (8 of 10)4/19/2008 7:54:34 PM

Please select the journal e-updates that you would like to receive:

Medical Journals

- ☐ American Family Physician
- ☐ American Journal of Medicine
- ☐ Annals of Internal Medicine
- ☐ Annals of Pharmacotherapy
- ☐ Archives of Internal Medicine
- ☐ BMJ
- ☐ JAMA
- ☐ Lancet
- ☐ Mayo Clinic Proceedings
- ☐ New England Journal of Medicine
- ☐ Stroke

Cardiology/Respiratory Journals

- ☐ American Heart Journal
- ☐ Canadian Journal of Cardiology
- ☐ Chest
- ☐ Thorax

Nephrology/Urology Journals

- ☐ American Journal of Kidney Diseases
- ☐ Journal of the American Society of Nephrology
- ☐ Nephrology, Dialysis, Transplantation
- ☐ Urology

Critical Care Journals

- ☐ Critical Care Medicine
- ☐ Intensive Care Medicine

Conclusion

Effective use of technology is required to selectively sort through the thousands of new professional literature citations that become available on a weekly basis. PubMed features such as Cubby can be used to accomplish this task. Allied Journal Club is a free Internet based medical literature alerting service that is simple to use and delivers email notification of new content availability for many major pharmacy and medical journals. PubMed provides access to citations and abstracts from thousands of journals but requires more effort to use than AJC. However, AJC provides content alerts from a more limited selection of journals. Either PubMed or AJC is an effective journal based literature screening method that can be customized to readers needs. The next installment of this series will outline techniques whereby health professionals can keep aware of developments in particular disease states or "therapeutic topics".

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ISSN 1492-2525

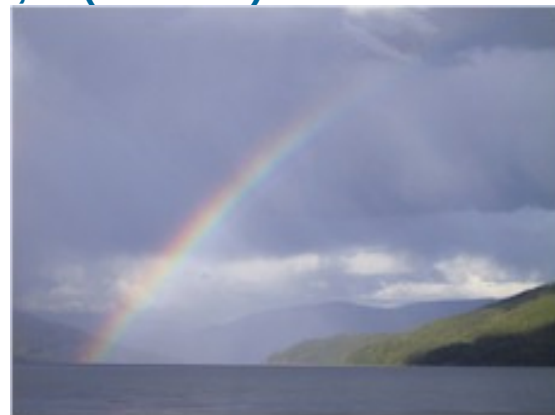
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Editorial

- Pharmacists and Potential Conflicts of Interest - Doing the Right Thing
Peter J. Jewesson



Email to the Editors

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- Readers respond to "Pharmacist Scope of Practice: A Response to the 2002 ACP-ASIM Position Paper"

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**Updated
December 12, 2002**

Editorial

Pharmacists and Potential Conflicts of Interest - Doing the Right Thing

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Perhaps you have read the recent article in the [New York Times](#) about the U.S. Government (specifically the [U.S. Department of Health & Human Services](#)) warning the pharmaceutical industry that they must not offer any financial incentives to any health care professional that would entice them to prescribe or recommend their products. (1,2) A laudable goal, but extremely difficult to execute. According to the author, the government has informed the manufacturers that currently employed marketing practices may contravene federal fraud and abuse laws. New standards have apparently been developed in an attempt to address this complex issue. These new standards raise the thorny issue of health care professionals and competing interests, otherwise known as "conflict of interest" (COI).

What is a COI? According to Michael McDonald, Director, Centre for Applied Ethics, University of British Columbia, a COI can be defined as a situation in which a person, such as a public official, an employee, or a professional, has a private or personal interest sufficient to appear to influence the objective exercise of his or her official duties. (3) A COI generally involves the abuse of the trust people have in professionals and tends to not only injure the relationship with a particular client or employer, but also damages the profession. There are 3 key elements to a COI: 1) a private or personal interest (e.g. financial benefit); 2) an official duty (i.e. duties you have because you have an office, or act in an official capacity and involves obligations to clients, employers or others that exceed private or personal interests and; 3) an interference with the objective and independent judgment that professionals are expected to provide. An "apparent" COI arises when a reasonable person would think that the professional's judgment is likely to be compromised, whereas a "potential" COI involves a situation that may develop into an actual COI. An "actual" COI exists when professional judgment concerning a primary interest has been unduly influenced by a secondary interest. (3)

Some general examples of financial relationships that can lead to an apparent COI would include investments, consultation work, research funding, support to organize an educational program, conference travel support, speaking honorariums and gifts. "Influence peddling" or the soliciting of benefits in exchange for using your influence to unfairly advance the interests of a particular party, and use of confidential information for the purchase of products (e.g. drug stocks) based upon knowledge gained through confidential information represent two forms of a COI that are, unfortunately, all too common.

Consider these hypothetical scenarios:

- You are on a federal committee and charged with determining whether a drug is a "breakthrough medication" for the purpose of national drug pricing. You are also a paid consultant for the

patentee of this product.

- You accept an invitation to attend an all expenses paid 3-day continuing education event in Lisbon, Portugal. The agenda will focus on the management of hepatitis include a 1-hour seminar each day, followed by an extensive social events agenda. Your spouse is invited. You will be expected to participate in the creation of "clinical practice guidelines" for hepatitis. A company who holds the patent on one of the competing drugs will sponsor the entire program.
- You attend a small group industry-sponsored dinner talk at a swank location, and receive a token gift of an expensive pen emblazoned with a product name. You were invited as you are considered to be a local opinion leader. You carry this coveted pen to rounds the next day and show it to your colleagues, including your new pharmacy residents.
- As the pharmacy director of a large hospital, you give permission for pharmaceutical reps to join the health care team at bedside, to review medical charts and discuss medication choices. In turn, your department will receive some expensive computer/projector equipment.
- As the pharmacy director of a large hospital, you agree to meet 3 reps this week to discuss new products. The first will be at 0745hrs on your way to work. You'll meet at the EZ Fill gas station and she'll pay for the fill up while talking to you about her new drug. The second will be at a Mr. Lube outlet on the way home tomorrow. He will pick up the tab for the oil change in exchange for your time. The third will be at the local Ho Lee Chow take out restaurant. The rep will pay for the order and pitch her product while you wait.
- You are contacted by a marketing group to complete a telephone survey. It will require 20 minutes of your time and the questions relate to lipid formulation amphotericin B prescribing in your hospital. You will receive \$200 for your participation and will be contacted at work mid morning.
- You have acted as a principal investigator for an industry-sponsored drug bioequivalence trial. Preliminary results do not favour the sponsor's drug. The sponsor isn't happy. They inform you that they now believe the study methodology was flawed and do not wish the data to be published. They also inform you that you will receive the full grant funds promised.
- You are invited by a well known journal to write a review paper on a new drug class. The journal will pay you \$1000 for your effort. You learn that the supplement is sponsored by a drug company and that they will be scrutinizing and approving the content before publication. You have a financial relationship with several of the patentees of these products. They have paid your speaker honorariums in the recent past.
- You sign a contract with a drug company to undertake research on their new drug. The contract contains a 3-year gag clause to prevent unauthorized release of any findings. Your hospital did not scrutinize the contract before signing.

While hypothetical, these scenarios are actually based upon descriptions of events that have reported in the literature, personal communication or experience. Every one of them represents a potential COI. Check out www.nofreelunch.org if you are interested in more examples and literature citations.

Gifts and other financial "sweeteners" constitute to another form of EBM, namely "Entrée-Based Medicine". These enticements trigger the "reciprocity rule" or the inherent social obligation to reciprocate when an unsolicited gift is received. (4) When a gift is accepted, a relationship and obligation is implicit. These enticements influence behaviour either directly or, similar to tobacco, on a secondhand basis. And, of course, these gifts cost money, and patients will eventually have to pay the bill. Finally, gifts can erode professional values and damage the public image. Not surprisingly, patients tend to feel that gifts to physicians are more influential and more inappropriate than do physicians themselves. (5)

Wazana recently published the results of an unfunded study in which he conducted a literature search to characterize the relationship between physicians and the pharmaceutical industry. (6) He identified 539 studies that met his search terms, of which 29 were deemed "relevant" in that they contained quantitative data and were published in a peer-reviewed journal. In summary, he found that interactions with industry were generally endorsed; the average frequency of encounter was 4/month; interactions resulted in increased formulary requests and prescribing changes; continuing education programs sponsored by industry preferentially highlighted sponsor products and resulted in attendees increased prescribing of sponsor drug; gifts positively influenced attitude towards sponsor. Unfortunately, he also determined that there are no published studies using patient outcome measures to determine the ultimate impact of this relationship.

Hospital pharmacists are being placed in a potential COI position more often than ever before. No doubt this relates directly to the significant and increasing influence and involvement we have in direct patient care, formulary management, patient education, education of other health care professionals, and drug-related research. As our responsibilities increase, so to does our risk for a COI. The ACP-ASIM recently released a position paper on physician-pharmaceutical industry relations. (7) They state that "...physicians frequently do not recognize that their decisions have been affected by commercial gifts and services and in fact deny industry's influence...research, however, shows a strong correlation between receiving industry benefits and favoring their products...". Why should we expect anything different of hospital pharmacists?

In contrast, the 2001 Canadian Society of Hospital Pharmacists guidelines for the relationship between health care facility pharmacists and the pharmaceutical industry simply state that "...the relationship between pharmacists and the industry can be beneficial to both parties..." and that the "...lines of communication should be kept open in a spirit of cooperation and coordination...". (8) Nowhere in the preface and scope of this position paper does it state that pharmacists must retain an arm's length relationship with industry to ensure objectivity. Perhaps an amendment is in order?

How do you determine if you are in position of a potential COI? Start by asking yourself some simple questions. Has the definition been met? Has your objectivity been compromised? Would relevant others (employer, clients, colleagues, or the general public) trust your judgment if they knew you were in this situation? Would you identify your involvement on your CV? Would you let your mother know?

What should you do if you find yourself in position of COI (potential, actual)? First off, recognize that it takes skill and good judgment to recognize a COI as private and personal interests can cloud objectivity. (3) It is often easier to recognize when others are in a conflict, than when you are. Experts generally recommend that you start by talking to a trusted colleague or friend when in doubt. It's also a good idea for you to re-familiarize yourself with existing professional guidelines, even if they are often somewhat dilute in nature. As soon as you recognize that you are in (or are headed for) a potential or actual COI situation, the right (i.e., ethical) thing to do is to get out of the situation, or, if you can't, make it known to all affected parties your private interest and preserve the trust essential to professional objectivity. (3)

According to recent Gallop polls, pharmacists are currently in a position that is envied by all other professionals. Over the past decade or more, we have been the top rated professional for honesty and ethics. (9) In fact, the public consistently rates the pharmacy profession higher than the medical

profession. This is not something that we should take lightly, rather it is something we should work hard to preserve. While I suspect that the public was thinking about their often-visited community pharmacists, rather than hospital pharmacists when completing these surveys, I think it would be safe to extrapolate the results to our profession as a whole. When compared to community pharmacists, institutional practitioners are actually uniquely situated to function as bioethical watchdogs. Institutional pharmacists are typically salaried public servants and their income is not dependent on sale of drug products. In fact, they routinely work towards reducing drug use in their practice setting and control the availability of drugs through the use of selective formularies, prescribing guidelines and restrictions and intensive continuing education. Let's recognize the trust the public has already placed in us and consider ourselves as bioethical watchdogs. In doing so, think carefully about your actions. Take your expanding professional responsibilities seriously and remember who you work for. Be "untouchable" and do the "right thing". Continue to be a profession that the public can rely on for objective and independent drug therapy expertise.

In summary, my hat goes off to the U.S. Department of Health & Human Services for their timely warning. Perhaps they should also be reminding the health care professionals that they should not accept these enticements. "With regards to my own status, I must admit to placing myself in a position of potential COI on a few occasions during my 24 years of practice, most of these occurring early in my career when ignorance was bliss. However, I now accept that, being human, I too am vulnerable to influence. Considering this inherent fallibility, I have taken actions, wherever possible, to minimize any apparent, potential or actual conflict of interest. I'm not on any industry advisory boards, not a paid industry consultant, don't speak at drug company events, nor have I financial interest in the sales of any drug product. How clean is your slate?

Peter J. Jewesson, PhD FCSHP
Publishing Co-Editor, Journal of Informed Pharmacotherapy

J Inform Pharmacother 2002;11:1.

This editorial is based upon a presentation given by Dr. Jewesson at the August 12, 2002 Canadian Society of Hospital Pharmacists Annual General Meeting, Vancouver BC, Canada.

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Reader Responses to the Editorial, "Pharmacists and Potential Conflicts of Interest - Doing the Right Thing"

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This view is commendable, albeit most difficult to follow. As a physician on the pharmacy committee of a large community hospital, I can tell you that our pharmacists use cost saving rather than evidence-based results in product acquisition. Is that any better or more ethical?

Gary Witman MD
Physician, Good Samaritan Medical Center

Once again I applaud Dr. Jewesson for a refreshing and courageous editorial. The issue of conflict of interest (COI) is an important one and has huge consequences, both in costs to the health care system as well the cost to the professional integrity of the individuals involved. If there ever was a belief that, by virtue of our professional training, pharmacists and other health professionals somehow acquired a sense of ethical conduct, that belief has been severely challenged. The "conscience" was once described to me as a three cornered wheel that spins in our heads. When we are first exposed to a moral or ethical dilemma, the corners cut in and hurt as they spin. This is the "pang of conscience" and, hopefully, we make the ethical decision, the wheel stops spinning and it stops hurting. But if we fail to heed the warning, take the unethical road and allow the corners to chafe continuously, the sharp corners eventually wear down and it doesn't hurt as much anymore. I believe that the temptations thrown at us every day from Big Pharma have worn the corners down permanently in many health professionals and the constant barrage of bribes and gimmes don't ever register as unethical.

I find it interesting that, while many hospitals have incorporated disclosure statements into their formulary application process that force physicians to disclose their ties to drug industry when applying for formulary status for a drug, the same disclosure requirement is not applied to the pharmacists involved in the same formulary process. Are we pharmacists somehow immune to the solicitations of

the drug industry or morally superior to physicians so that disclosure is unnecessary? Somehow I don't think so.

It is a sad commentary on our profession, and maybe on society in general, that many individuals do not perceive their actions as unethical or in potential COI. Pharmacists, especially those in a direct position of influence on drug utilization such as a Clinical Specialists or DUE pharmacists, must not only maintain absolute objectivity and impartiality, but they must be perceived to be acting objectively and impartially. It is not good enough to say one is impervious to commercial influence, and that that free round of golf or dinner or other gimme has no effect on one's behavior. We must all realize that those freebies are paid for by someone - the consumer or the taxpayer - and that by accepting them, an implicit obligation to the donor (i.e. drug company) has been established. One becomes tainted from the moment they accept the gift.

So who is at fault for the current ethical dilemma? Pharmacists and physicians point the finger at drug industry for offering bribes and resorting to influence-peddling, while the drug companies complain that they are forced into this behavior because physicians and pharmacists expect it - in fact demand it. In fact both are true and we are all (bribers and bribees alike) somewhat to blame. The problem is so ubiquitous and entrenched, that it is difficult for most people to distinguish ethical boundaries as they pertain to their relationship with the drug industry. Where do you draw the line? Is it OK to have a drug rep buy you lunch, or even a cup of coffee? Or is the line drawn at a round of golf, or a dinner or a hockey game or ...? In my view, the line can be drawn in only one place, and that is to refuse all gifts from the drug industry including that cup of coffee. Once you move the line anywhere else, it becomes arbitrary, and it is just as easy to equate a \$100 hockey ticket or a \$60 round of golf with a \$2 cup of coffee as it is a \$1000 all expenses paid weekend at the You-Name-it Fishing Lodge. The ACP-ASIM guidelines states "It is not just lavish amenities that are in question. The acceptance of even small gifts can affect clinical judgment and heighten the perception (as well as the reality) of a conflict of interest" I have little faith that voluntary guidelines for the relationship between health care professionals and the pharmaceutical industry such as those set by the ACP-ASIM and CSHP will be the answer. Unless we all take COI seriously and actively and continuously monitor our behavior with the pharmaceutical industry for potential COI, the only alternative, I fear, is government legislation mandating an arms-length relationship with the industry. We have to do much better than we are doing now. We must be continuously vigilant of the threats to our professionalism and independent judgment with respect to the care of our patients and the exercising of our official duties. We must not let the corners of our conscience wear down.

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Issues in Pharmacotherapy Practice

Pharmacokinetic Pearls for the Clinical Pharmacist

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Abstract

Background: The interpretation of imperfect data is one of the challenges of clinical pharmacokinetics. The equations and theorems used to guide our pharmacokinetic assessment of the patient often assume perfection, while the practicing clinician is faced with many discrepancies from dose to dose, drug to drug, and even institution to institution.

Objectives: To determine whether there is a clinically relevant difference between a peak vancomycin concentration drawn 1 hour after the end of a 1-hour infusion and a back-extrapolated theoretical concentration. To determine whether non-steady-state aminoglycoside concentrations drawn around the third dose after small changes in dosing intervals can be interpreted using steady-state equations.

Methodology: Computer simulations of hypothetical scenarios were performed.

Results: For the majority of patients, there is no clinically relevant difference between peak vancomycin concentrations drawn 1 hour after the end of a 1-hour infusion and back-extrapolated theoretical concentrations. The only exception is in patients with a half-life of vancomycin shorter than 3.11 hours. These recommendations apply only to patients for whom a 1-hour post vancomycin concentration is appropriate. For the majority of patients (who have aminoglycoside half-lives that are consistent with population estimates), clinicians can use steady-state equations to interpret non-steady-state

aminoglycoside concentrations drawn around the third dose after minor derangements in dosing intervals. The only exception is in patients with a half-life of aminoglycosides longer than approximately 5 hours.

Conclusion: We have discussed two commonly-encountered pharmacokinetic scenarios and provided practical recommendations on how to interpret drug concentrations obtained during each situation.

J Inform Pharmacother 2002;11:300.

Introduction

The interpretation of imperfect data is one of the challenges of clinical pharmacokinetics. The equations and theorems used to guide our pharmacokinetic assessment of the patient often assume perfection, while the practicing clinician is faced with many discrepancies from dose to dose, drug to drug, and even institution to institution. In this article, we discuss two commonly-encountered pharmacokinetic scenarios and provide practical recommendations on how to interpret drug concentrations obtained during each situation. The purpose of this investigation is neither to debate the merits of therapeutic drug monitoring nor to examine the relationship between concentration and effect, but rather to highlight the relevance of utilizing imperfect data.

The Clinically Relevant Peak Concentration

Studies are inconsistent with regards to a standard sampling time of peak aminoglycoside concentrations. With conventional dosing (i.e., multiple-daily dosing), some pharmacists use the back-extrapolated aminoglycoside concentration (i.e., the theoretical concentration attained at the end of an intravenous infusion), while others rely on peak concentrations measured 0-60 minutes after a 30- to 60-minute intravenous infusion. (1-3) By convention, current practice patterns dictate that the clinically relevant aminoglycoside peak concentration be drawn 30 minutes after the end of a 30-minute infusion, (2) and thus, target ranges for aminoglycoside concentrations (values depend on the indication for treatment) refer to this peak. Aminoglycoside concentration monitoring with once-daily dosing has not been delineated clearly, (4) although if samples are drawn, the clinician must consider the prolonged distribution phase following administration of a once-daily dose. (5) One institution recommends that the first random concentration after a once-daily aminoglycoside dose be drawn 4 hours after completion of the infusion, based on pharmacokinetic studies in trauma patients and healthy volunteers. (2)

The evidence for peak vancomycin concentrations is even more conflicting. An overview suggested that the optimal sampling time for peak vancomycin concentrations was poorly defined due to its multi-compartmental pharmacokinetic characteristics. (6) As such, it was difficult to compare different nomograms, in which clinicians have measured peak concentrations 1, 2, or 3 hours after the end of a 1-hour intravenous infusion. (6)

Similarly, controversy exists among three local teaching hospitals as to definition of a clinically relevant peak vancomycin concentration. Guidelines at a 950-bed adult acute care facility recommend drawing vancomycin concentrations 3 hours after the end of a 1-hour infusion, and utilize this 3-hour post as their peak concentration (target 15 to 25 mg/L). (7) In contrast, pharmacists at another adult acute care hospital with 445 beds measure vancomycin concentrations 3 hours after the end of a 1-hour infusion (target 15 to 20 mg/L), and extrapolate back to the theoretical concentration at the end of the infusion. (8) This back-extrapolated concentration is then deemed the relevant peak (target 20 to 30 mg/L). (8) At a 400-bed, tertiary-care institution caring for maternity and pediatric patients, the peak vancomycin concentrations are drawn 1 hour after the end of a 1-hour infusion (target 20 to 40 mg/L). (9) Within each institution, some pharmacists may deviate from institutional protocol and use back-extrapolated theoretical concentrations to guide vancomycin therapy.

Since vancomycin is a time-dependent kill antibiotic, trough concentrations may be a more clinically significant surrogate marker. However, vancomycin peak concentrations may be of therapeutic value for select patient populations in whom it is useful to confirm that target concentrations have been attained. Moreover, all three local teaching hospitals have distinct recommendations for monitoring of vancomycin peak levels, creating controversy among practitioners who are faced with discrepancies from institution to institution, and even from pharmacist to pharmacist.

Objective

Our objective was to determine whether there is a clinically relevant difference between a peak vancomycin concentration drawn 1 hour after the end of a 1-hour infusion and a back-extrapolated theoretical concentration.

Methodology

Computer iterations using simulated data were performed using a Microsoft® Excel

(Microsoft Corporation, Redmond, WA) spreadsheet. A series of minimum concentrations ($C_{\min}$, defined as the vancomycin concentration immediately before the dose) were matched with a series of maximum concentrations ($C_{\max}$, defined as the theoretical vancomycin concentration extrapolated to immediately after the end of a 1-hour infusion) and concentrations 1 hour post end of infusion ($C_{1h \text{ post}}$, defined as the vancomycin concentration 1 hour after the end of a 1-hour infusion). An arbitrary number of simulations were performed to encompass concentrations within and out of the therapeutic range.

Two variables were fixed (i.e., $C_{\min}$ and either $C_{\max}$ or $C_{1h \text{ post}}$), to calculate the elimination rate constant (K) and elimination half-life ($t_{1/2}$) using standard pharmacokinetic equations. The remaining concentration (either $C_{\max}$ or $C_{1h \text{ post}}$) was calculated using Equation 1, where C refers to the lower concentration (i.e., $C_{1h \text{ post}}$), C_0 is the higher concentration (i.e., $C_{\max}$), K refers to the elimination rate constant, and t is the time of the infusion (i.e., 1 hour). All possible combinations of $C_{\min}$, $C_{\max}$ and $C_{1h \text{ post}}$ were tested.

$$C = C_0 \times e^{-Kt} \quad (\text{Equation 1})$$

The final step in the computer simulations involved calculation of the percentage difference between the values of $C_{\max}$ and $C_{1h \text{ post}}$ (ΔC , defined as percentage change in concentration between $C_{\max}$ and $C_{1h \text{ post}}$) using Equation 2. Since a total error of 25% associated with a single concentration (i.e., a sum of administration, documentation, rounding-off, sampling, analytical errors, etc.) would not be unexpected, we used a conservative threshold of 20% as our maximum allowable error (i.e., clinically irrelevant ΔC defined as $\leq 20\%$).

$$\Delta C = (C_{\max} - C_{1h \text{ post}}) / C_{\max} \times 100\% \quad (\text{Equation 2})$$

The computer simulations were repeated for 12-, 8-, and 6-hour vancomycin dosing intervals.

Results

Tables I, II, and III show the results of the computer simulations for 12-, 8-, and 6-hour vancomycin dosing intervals, respectively. The grey-shaded boxes represent fixed

concentrations, while the unshaded boxes represented calculated values. The yellow-shaded boxes denote clinically relevant $\Delta C > 20\%$.

Table I. Computer Simulations for 12-hour Vancomycin Dosing Interval.

$C_{\min}$ (mg/L)	$C_{\max}$ (mg/L)	$C_{1h \text{ post}}$ (mg/L)	ΔC (%)	K (h^{-1})	$t_{1/2}$ (h)
5.0	20.0	17.6	11.84	0.13	5.50
5.0	22.9	20.0	12.94	0.14	5.00
5.0	30.0	25.5	15.03	0.16	4.25
5.0	35.9	30.0	16.40	0.18	3.87
5.0	40.0	33.1	17.22	0.19	3.67
5.0	49.3	40.0	18.77	0.21	3.33
10.0	20.0	18.8	6.11	0.06	11.00
10.0	21.4	20.0	6.70	0.07	10.00
10.0	30.0	27.2	9.50	0.10	6.94
10.0	33.5	30.0	10.40	0.11	6.31
10.0	40.0	35.3	11.84	0.13	5.50
10.0	46.0	40.0	12.94	0.14	5.00
15.0	20.0	19.5	2.58	0.03	26.50
15.0	20.6	20.0	2.84	0.03	24.09
15.0	30.0	28.2	6.11	0.06	11.00
15.0	32.2	30.0	6.70	0.07	10.00
15.0	40.0	36.6	8.53	0.09	7.77
15.0	44.1	40.0	9.34	0.10	7.07

2.5	30.0	23.9	20.22	0.23	3.07
2.5	38.5	30.0	22.00	0.25	2.79
10.0	50.0	34.2	13.61	0.15	4.74
10.0	58.7	50.0	14.87	0.16	4.31

$C_{\min}$ = concentration immediately before the dose (i.e., true trough); $C_{\max}$ = concentration extrapolated to immediately after the end of the 1h infusion; $C_{1h \text{ post}}$ = concentration 1h after the end of a 1h infusion; ΔC = percentage change in concentration between $C_{\max}$ and $C_{1h \text{ post}}$; K = elimination rate constant; $t_{1/2}$ = elimination half-life

Table II. Computer Simulations for 8-hour Vancomycin Dosing Interval.

$C_{\min}$ (mg/L)	$C_{\max}$ (mg/L)	$C_{1h \text{ post}}$ (mg/L)	ΔC (%)	K (h ⁻¹)	$t_{1/2}$ (h)
5.0	20.0	16.4	17.97	0.20	3.50
5.0	25.2	20.0	20.63	0.23	3.00
5.0	30.0	23.2	22.58	0.26	2.71
5.0	40.4	30.0	25.82	0.30	2.32
5.0	40.0	29.7	25.70	0.30	2.33
5.0	56.6	40.0	29.29	0.35	2.00
10.0	20.0	18.1	9.43	0.10	7.00
10.0	22.5	20.0	10.91	0.12	6.00
10.0	30.0	25.6	14.52	0.16	4.42
10.0	36.0	30.0	16.73	0.18	3.78
10.0	40.0	32.8	17.97	0.20	3.50
10.0	50.4	40.0	20.63	0.23	3.00

15.0	20.0	19.2	4.03	0.04	16.86
15.0	21.0	20.0	4.68	0.05	14.45
15.0	30.0	27.2	9.43	0.10	7.00
15.0	33.7	30.0	10.91	0.12	6.00
15.0	40.0	34.8	13.07	0.14	4.95
15.0	47.1	40.0	15.08	0.16	4.24
2.5	30.0	21.0	29.88	0.35	1.95
2.5	45.4	30.0	33.91	0.41	1.67
10.0	50.0	39.7	20.54	0.23	3.01
10.0	65.4	50.0	23.53	0.27	2.58

$C_{\min}$ = concentration immediately before the dose (i.e., true trough); $C_{\max}$ = concentration extrapolated to immediately after the end of the 1h infusion; $C_{1h \text{ post}}$ = concentration 1h after the end of a 1h infusion; ΔC = percentage change in concentration between $C_{\max}$ and $C_{1h \text{ post}}$; K = elimination rate constant; $t_{1/2}$ = elimination half-life

Table III. Computer Simulations for 6-hour Vancomycin Dosing Interval.

$C_{\min}$ (mg/L)	$C_{\max}$ (mg/L)	$C_{1h \text{ post}}$ (mg/L)	ΔC (%)	K (h ⁻¹)	$t_{1/2}$ (h)
5.0	20.0	15.2	24.21	0.28	2.50
5.0	28.3	20.0	29.29	0.35	2.00
5.0	30.0	21.0	30.12	0.36	1.93
5.0	47.0	30.0	36.11	0.45	1.55
5.0	40.0	26.4	34.02	0.42	1.67
5.0	67.3	40.0	40.54	0.52	1.33

10.0	20.0	17.4	12.94	0.14	5.00
10.0	23.8	20.0	15.91	0.17	4.00
10.0	30.0	24.1	19.73	0.22	3.15
10.0	39.5	30.0	24.02	0.27	2.52
10.0	40.0	30.3	24.21	0.28	2.50
10.0	56.6	40.0	29.29	0.35	2.00
15.0	20.0	18.9	5.59	0.06	12.04
15.0	21.5	20.0	6.94	0.07	9.64
15.0	30.0	26.1	12.94	0.14	5.00
15.0	35.7	30.0	15.91	0.17	4.00
15.0	40.0	32.9	17.81	0.20	3.53
15.0	51.1	40.0	21.75	0.25	2.83
2.5	30.0	18.3	39.16	0.50	1.39
2.5	55.8	30.0	46.27	0.62	1.12
10.0	50.0	36.2	27.52	0.32	2.15
10.0	74.8	50.0	33.13	0.40	1.72

$C_{\min}$ = concentration immediately before the dose (i.e., true trough); $C_{\max}$ = concentration extrapolated to immediately after the end of the 1h infusion; $C_{1h \text{ post}}$ = concentration 1h after the end of a 1h infusion; ΔC = percentage change in concentration between $C_{\max}$ and $C_{1h \text{ post}}$; K = elimination rate constant; $t_{1/2}$ = elimination half-life

Discussion

The computer simulations illustrate that for the majority of the hypothetical scenarios, there is no clinically relevant difference between a peak vancomycin concentration

drawn 1 hour after the end of a 1-hour infusion and a back-extrapolated theoretical concentration. A 1-hour post concentration would be appropriate in patients who do not have a prolonged distribution phase (e.g., patients without renal impairment or severe congestive heart failure). (2), (10) In these patients, the only situations where ΔC was greater than 20% were cases in which the calculated $t_{1/2}$ of vancomycin was shorter than 3.11 hours. This can be mathematically proved using Equation 1, assuming $C = C_{1h \text{ post}} = 0.8$, $C_0 = C_{\max} = 1$ (thus $\Delta C = 0.2$ or 20%), and $t = 1$ hour.

$$C = C_0 \times e^{-Kt} \quad (\text{Equation 1})$$

$$C_{1h \text{ post}} = C_{\max} \times e^{-Kt}$$

$$0.8 = 1 \times e^{-K \times 1}$$

$$\ln(0.8) = -k$$

$$k = 0.223 \text{ h}^{-1}$$

$$t_{1/2} = 3.11 \text{ h}$$

It is impossible to predict vancomycin's $t_{1/2}$ *a priori*; thus, the threshold 3.11-hour $t_{1/2}$ cannot be utilized *a priori* to predict whether the 1-hour post and back-extrapolated concentrations will be clinically different. However, if a patient does exhibit a calculated vancomycin $t_{1/2}$ of shorter than 3.11 hours (using the 1-hour post and trough concentrations), the pharmacist should be aware that there is likely a greater than 20% difference between the 1-hour post and back-extrapolated concentrations. In this scenario, it may be appropriate to use the back-extrapolated concentration rather than the 1-hour post concentration to guide therapy.

One caveat is that a 1-hour post concentration may not be suitable for patients who have a prolonged distribution phase (e.g., patients with renal impairment or severe congestive heart failure). (10)

Recommendations

For the majority of patients, there is no clinically relevant difference between peak vancomycin concentrations drawn 1 hour after the end of a 1-hour infusion and back-extrapolated theoretical concentrations. The only exception is in patients with a half-life of vancomycin shorter than 3.11 hours; in this case, the difference between peak concentrations drawn 1 hour after the end of a 1-hour infusion and back-extrapolated theoretical concentrations is greater than 20%. In patients with a suspected half-life shorter than 3.11 hours, it may be appropriate to use the back-extrapolated

concentration to guide therapy. These recommendations only apply to patients for whom a 1-hour post vancomycin concentration is appropriate.

The Effect Changing Dose Intervals

The fundamental concept of steady state refers to a situation where administration of multiple doses of a drug at fixed intervals results in drug accumulation until the rate of elimination is equal to the rate of administration. However, initial doses often are given in changing, not fixed, intervals in order to comply with standardized medication administration times; despite this, drug concentrations often are ordered with the third dose, regardless of changing intervals. Therefore, it may be unclear to the clinician whether these non-steady-state drug concentrations can be interpreted. This scenario will be illustrated using aminoglycosides as a prototype.

Objective

Our objective was to determine whether non-steady-state aminoglycoside concentrations drawn around the third dose after small changes in dosing intervals can be interpreted using steady-state equations for calculation of pharmacokinetic parameters. Specifically, we assumed that a gentamicin 80 mg IV every 8 hours order was given as follows: first dose administered from 00:00 to 00:30; second dose administered from 10:00 to 10:30; third dose administered from 17:00 to 17:30; and subsequent doses administered every 8 hours. Also we assumed that our patient weighed 70 kg and had a volume of distribution of 17.5 L (0.25 L/kg). This exercise applies only if these specific assumptions are made.

Methodology

Computer simulations were performed using a Microsoft® Excel (Microsoft Corporation, Redmond, WA) spreadsheet. A series of half-lives ($t_{1/2}$) and their corresponding elimination rate constants (K) were specified, and then the concentration at 12 time points over a 42-hour time period (00:00, 00:30, 10:00, 10:30, 17:00, 17:30, 01:00, 01:30, 09:00, 09:30, 17:00, 17:30) were determined. Aminoglycoside concentrations immediately before the next dose ($C_{\min}$) were calculated using Equation 1, where C_0 is the concentration at the end of the infusion, and t is the time between the end of the infusion and the next dose. Theoretical aminoglycoside concentrations extrapolated to immediately after the end of an 0.5-hour infusion ($C_{\max}$) were calculated using Equation 3, where $C_{\min}$ is the concentration immediately before the dose, t is the infusion time (i.

e., 0.5 hour), k_0 refers to dosing rate (i.e., 80 mg / 0.5 hour), V is the volume of distribution (i.e., 17.5 L), and K refers to the elimination rate constant.

$$C_{\max} = (C_{\min} \times e^{-Kt}) + (k_0/VK [1 - e^{-Kt}])$$

(Equation 3)

Finally, steady-state equations (erroneously assuming steady state) were utilized to calculate $t_{1/2}$ and K with concentrations drawn around the third dose; these values were then compared with the original assumed $t_{1/2}$ and K .

Results

Table IV shows the results of the computer simulations for an assumed aminoglycoside $t_{1/2}$ of 3.00 h and K of 0.23 h⁻¹. If the steady-state equations had been used (erroneously assuming that the third dose had been at steady state), $t_{1/2}$ would have been 3.24 h and K 0.21 h⁻¹. In actuality, true steady state was reached with the fifth dose (i.e., the dose at 09:00 on the second day of therapy). For a shorter assumed $t_{1/2}$ of 1.00 h, $t_{1/2}$ calculated using steady-state equations was 1.15 h. Steady state was reached sooner in this scenario with the fourth dose (i.e., the dose at 01:00 on the second day of therapy). In the case of a longer assumed $t_{1/2}$ of 5.00 h, $t_{1/2}$ calculated using steady-state equations was 4.88 h. In contrast, steady state was not reached until the sixth dose (i.e., the dose at 17:00 on the second day of therapy). Simulations for $t_{1/2}$ of 2.00 h, 10.00 h, and 20.00 h were also performed.

Table IV. Computer Simulations for Changing Aminoglycoside Dose Intervals^a.

Time	Concentration (mg/L)
00:00	0.00
00:30	4.32
10:00	0.48
10:30	4.75
17:00	1.06
17:30	5.26
01:00	0.93
01:30	5.15
09:00	0.91
09:30	5.13
17:00	0.91
17:30	5.13

^a Assumptions: 70 kg patient; volume of distribution 17.5 L (0.25 L/kg); dose 80 mg given over 0.5 hours; half-life 3.00 hours.

Discussion

The computer simulations illustrate that for patients with an aminoglycoside $t_{1/2}$ of 3.00 h and changing dose intervals (first two doses given 10 hours apart and the third dose 7 hours later), non-steady state aminoglycoside concentrations can be interpreted using steady-state equations for calculation of pharmacokinetic parameters. The same is true with a shorter aminoglycoside $t_{1/2}$ of 1.00 h, as steady state is reached sooner.

The simulations also show that when aminoglycoside $t_{1/2}$ was prolonged (≥ 5 hours), the length of time to reach steady state was greater. In this case, a larger discrepancy between assumed $t_{1/2}$ and calculated $t_{1/2}$ (using concentrations around the third dose and steady-state equations) would occur; presumably, the clinician would be administering aminoglycoside doses utilizing a longer dosing interval.

It is impossible to predict an aminoglycoside's $t_{1/2}$ *a priori*; thus, the threshold 5-hour $t_{1/2}$ cannot be utilized *a priori* to predict whether the assumed and calculated $t_{1/2}$ will be clinically different. However, if it is suspected that a patient will exhibit a calculated aminoglycoside $t_{1/2}$ of longer than 5 hours, the pharmacist should be aware of the limitations of concentrations drawn around the third dose. In this scenario, it may be appropriate to obtain concentrations with a later dose, or to use random concentrations (e.g., two concentrations drawn at least one $t_{1/2}$ apart to calculate K and $t_{1/2}$) to guide dosing and respond to changes in patient status.

Recommendations

For the majority of patients (who have aminoglycoside half-lives that are consistent with population estimates), clinicians can use steady-state equations for calculation of pharmacokinetic parameters in the interpretation of non-steady state aminoglycoside concentrations drawn around the third dose after minor derangements in dosing intervals. The only exception is in patients with a half-life longer than approximately 5 hours; in this case, the length of time to reach steady state is greater, and the difference between assumed half-life and calculated half-life (using steady-state equations) is larger. In patients with a suspected half-life of longer than 5 hours, it may be

appropriate to obtain concentrations with a later dose or to use random concentrations to guide dosing.

Conclusion

In this article, we have discussed two commonly-encountered pharmacokinetic scenarios and provided practical recommendations on how to interpret drug concentrations obtained during each situation.

Acknowledgement

Many thanks to the pharmacists at Children's and Women's Health Centre of British Columbia for submitting pharmacokinetic issues observed in their clinical practice. These ideas became the basis for this article.

Authors Competing Interests

None declared.

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Evidence Based Snapshots

The Journal of Informed Pharmacotherapy 2002;11:150.

Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients with Septic Shock

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Reviewer's profession/specialty: Associate Editor, Journal of Informed Pharmacotherapy

Original Citation

Annane D, Sébille V, Charpentier C, Bollaert P, François B, Korach J, Capellier G, Cohen Y, Azoulay E, Troché G, Chaumet-Riffaut P, Bellissant E. Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock. JAMA 2002;288:862-71 [PubMed Citation](#)

Overall Study Question

These investigators assessed whether low doses of corticosteroids could reduce mortality when given to patients with septic shock. The main endpoint was the 28-day survival in patients with relative adrenal insufficiency.

Patients

299 patients fulfilling the criteria for septic shock. Their average age was 61 and approximately 34% were female.

Treatment

Patients were randomized to receive either placebo or hydrocortisone 50 mg IV every 6 hours plus fludrocortisone 50 mcg daily for 7 days. All patients received a corticotropin test to identify relative adrenal insufficiency. Relative adrenal insufficiency (non-responders) was defined by a response of 9 mcg/dL or less.

Duration

The duration of follow up was 28 days.

Results

	28-day mortality (%)			ICU mortality (%)			Not yet withdrawn from vasopressor therapy at 28 days (%)		
	All*	R	NR	All**	R	NR	All	R	NR
Corticosteroids	55	61	53	60	67	58	45	50	43
Placebo	61	53	63	68	59	70	57	47	60
Relative Risk Reduction	10	NSS	16	12	NSS	17	21	NSS	28
Absolute Risk Reduction	6		10	8		12	12		17
NNT	17		10	13		8	8		6

* p = 0.09, ** p = 0.06

NR= non responders/relative adrenal insufficiency, R = responders to corticotropin test, NSS = not statistically significant

Other results

Adverse events rates were similar for each group.

How does this study contribute to the drug therapy of septic shock?

This study suggests that corticosteroids given to patients with septic shock and adrenal insufficiency decreases 28-day and ICU mortality.

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Evidence Based Snapshots

The Journal of Informed Pharmacotherapy 2002;11:151.

Ginkgo for Memory Enhancement

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Reviewer's profession/specialty: Associate Editor, Journal of Informed Pharmacotherapy

Original Citation

Solomon PR, Adams F, Silver A, Zimmer J, DeVeayx R. Ginkgo for memory enhancement - a randomised controlled trial. JAMA 2002;288:835-40. [Pubmed Citation](#)

Overall Study Question

These investigators looked to determine whether or not ginkgo improves memory in the elderly.

Patients

230 community dwelling volunteers in generally good health. Their average age was 68 (range 60-82) and 59% were female.

Treatment

Patients were randomized to receive either placebo or ginkgo 40 mg orally three times daily for 6 weeks. Outcome measures consisted of 14 tests of learning and memory, attention and concentration, expressive language, and a memory questionnaire. In addition, a global evaluation by spouse, relative or friend was conducted.

Duration

The duration of follow up was 6 weeks.

Results

None of the differences between the groups were statistically different. Of the 14 tests, seven of the point estimates favoured ginkgo and seven favoured placebo.

Other Results

There was no monitoring of adverse effects.

How does this study contribute to the drug therapy of memory in the elderly?

This study suggests that ginkgo at a dose of 40 mg orally three times daily for 6 weeks does not enhance memory in otherwise healthy elderly adults. Drug-associated adverse effects with this regimen was not assessed.

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Evidence Based Snapshots

The Journal of Informed Pharmacotherapy 2002;11:152.

Warfarin, Aspirin, or Both After Myocardial Infarction

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Reviewer's profession/specialty: Associate Editor, Journal of Informed Pharmacotherapy

Original Citation

Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin or both after myocardial infarction. NEJM 2002;347: 969-74

[PubMed Citation](#)

Overall Study Question

These investigators assessed whether warfarin, aspirin, or a combination of aspirin and warfarin would reduce a combination of death, non-fatal reinfarction, and thromboembolic stroke.

Patients

3,630 patients fulfilling the criteria for acute myocardial infarction. Their average age was 60 years and approximately 75% were male.

Treatment

Patients were randomized in an open label fashion to receive either warfarin (adjusted to an INR of 2.8-4.2), aspirin (160 mg), or aspirin (80 mg) PLUS warfarin (adjusted to an INR of 2.0-2.5) daily.

Duration

The mean duration of follow up was 4 years.

Results

	Reinfarction (%)	Thromboembolic stroke (%)	Death (%)	Reinfarction, thromboembolic stroke, death (%)	Major bleeds	Minor bleeds
Warfarin	7.4	1.4	7.9	16.7	2.7	8.5
Aspirin	9.7	2.7	7.6	20	0.7	3.2
Warfarin/aspirin	5.7	1.4	7.9	15	2.3	11
Relative Risk Reduction	41*	48**	NSS	25*	285***	Stats not done
Absolute Risk Reduction	4*	1.3**		5*	2***	
NNT	25*	77**		20*	50***	

* = warfarin/aspirin versus aspirin

** = warfarin versus aspirin and warfarin/aspirin versus aspirin

*** = harm increase - warfarin versus aspirin

NSS = not statistically significant

How does this study contribute to the drug therapy of myocardial infarction?

This study suggests that a combination of aspirin (80 mg) PLUS warfarin, or just warfarin (adjusted to achieve a higher INR value), decreases the chance of a combination of reinfarction, thromboembolic stroke and death by 5% in patients with myocardial infarctions when compared to the use of higher dose aspirin (160 mg) therapy. However, major bleeds will occur more frequently in patients receiving warfarin with higher INR values.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2002;11:200.

Perindopril and Stroke Prevention: Are We Really Making PROGRESS?

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Reviewers_Specialty: Clinical Pharmacist - Neurosciences

Original Citation

PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. Lancet 2001;358:1033-41 [PubMed Citation](#)

Overall Study Question

The purpose of this study was to determine the effects of a blood-pressure lowering regimen (perindopril plus indapamide vs. perindopril alone) on the risk of stroke and other major vascular events among patients with a history of stroke or transient ischemic attack (TIA). The 6,105 patients included were those with a history of stroke or TIA within the past 5 years. They could have no clinical indication for an ACE inhibitor, and no contraindication to an ACE inhibitor. There were no blood pressure-related criteria for entering the study, however patients with uncontrolled hypertension were recommended to receive antihypertensive therapy before entry into the trial. Patients were also recommended to be clinically stable for 2 weeks prior to entry into the study.

The primary study outcome was fatal or non-fatal stroke. Secondary outcomes included a combined endpoint of fatal or disabling stroke; total major vascular events (composite of non-fatal stroke, non-fatal myocardial infarction, or death due to any vascular cause); total and cause-specific death; and hospital admissions.

Potentially eligible patients entered a 4-week pre-randomization run-in period during which they received open-label perindopril (2 mg PO daily for 2 weeks, then increased to 4 mg PO daily for 2 weeks). If they adhered to and tolerated this regimen, they were randomly assigned to continued active therapy or matching placebo. In the active therapy group, patients received perindopril 4 mg PO daily alone or perindopril 4 mg PO daily plus indapamide 2.5 mg PO daily. In the placebo group, patients received either double placebo or single placebo. This was a "flexible" regimen, meaning that prior to randomization, the responsible physician was asked about his or her intentions with respect to treatment intensity. Those patients whom the physician found no specific indication for or contraindication to treatment with a diuretic were randomized to either double active therapy (perindopril plus indapamide) or double placebo. The remaining patients received either single active

therapy (perindopril) or single placebo. This flexibility allowed the authors to stratify by the intention to use single therapy or combination therapy.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Partially. Although patients were randomized to either placebo or active therapy, there was no randomization between single or combination therapy.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Of the 7,121 patients who entered the run-in phase, 1016 (14%) were either ineligible or withdrew. The main reasons for withdrawal were dizziness or hypotension (3.4%), cough (2.7%), other suspected intolerance (2.3%) or patient's decision (2.0%).

Of the remaining 6,105 patients, 3,544 were randomized to placebo and 3,051 to active therapy. Two patients in the active group and one patient in the placebo group were lost to follow-up.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Partially. While patients and investigators appear to have been blinded as to whether or not a patient was receiving active therapy or placebo, they do not appear to have been blinded as to whether patients were receiving single or combination therapy. Aside from the use of identical appearing placebo tablets, specific blinding procedures for all study personnel are not elaborated upon.

4. Were the groups similar at the start of the trial?

The active treatment and placebo groups appeared to be similar. However, patients in the combination group tended to be younger, were more likely to be men, had higher blood pressures at entry, were more likely to have a history of hypertension, were more likely to have coronary heart disease, and were recruited sooner after their qualifying cerebrovascular event.

5. Aside from the experimental intervention, were the groups treated equally?

Yes. Aside from the pre-specified stratification into combination therapy or single therapy, the groups appear to have been treated similarly.

What were the Results?

1. How large was the treatment effect?

For the primary outcome, 307 patients in the active group (10%) had a stroke during follow-up as compared to 420 (14%) patients in the placebo group ($p < 0.0001$). There was no evidence of heterogeneity in the size of the hazard ratios between subgroups defined by type of stroke (ischemic vs. hemorrhagic) or the time interval between initial stroke and enrolment (<6 months or 6 months to 5 years).

For secondary outcomes, there were fewer fatal and disabling strokes in the active group compared to placebo (Relative risk reduction [RRR] 33% with 95% confidence interval [CI] 15 to 46; Event rates [ER] 4% vs. 6%). Total major vascular events (composite of MI, stroke, and vascular death) were also reduced in the active group (RRR 26%, 95% CI 16 to 34, ER 15% vs. 20%). There was no difference in total mortality, however the proportion of patients admitted to hospital was statistically significantly lower in the active group (RRR 9%, 95% CI 1 to 15; ER 41% vs. 44%).

The active combination (perindopril + indapamide) group also experienced a reduction in stroke risk compared to placebo combination (RRR 43%, 95%CI 30 to 54, ER 8.5% vs. 14.4%). The stroke rate in the active single therapy (perindopril) group did not differ from the placebo single therapy group (RRR 5%, 95%CI -19 to 23, ER 12.3% vs. 12.8%). As well, patients who received combination therapy had lower rates of any major cardiovascular event when compared to placebo (RRR 40%, 95% CI 29 to 49, ER 13% vs. 21%), whereas those receiving single therapy did not (RRR 4%, 95% CI -15 to 20, ER 17.7% vs. 18.5%). The authors report significant heterogeneity ($P < 0.001$) in the sizes of these treatment effects.

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The overall average difference in blood pressure reduction (systolic/diastolic) was 9/4 mm Hg, favouring those in the active treatment group as compared with those in the placebo group. Those assigned to combination therapy had a greater reduction in blood pressure (12.3/5.0 mm Hg) compared to those assigned single therapy (4.9/2.8 mm Hg).

The reductions in stroke risk and major cardiovascular events were of similar size in both hypertensive (SBP ≥ 160 mm Hg or DBP ≥ 90 mm Hg) and non-hypertensive patients. Again, this risk was significantly reduced in patients on combination therapy, and not in the single therapy group.

2. How precise was the estimate of the treatment effect?

The risk of stroke was reduced by an absolute reduction of 4% when comparing active therapy to placebo (i.e. 10% vs. 14%). My calculation of the 95% confidence intervals for this ARR is 2% - 6% (NNT 17 - 50).

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

The patients enrolled are representative of stroke patients and the results appear to have been appropriately reported.

2. Were all clinically important outcomes considered?

Although the efficacy endpoints appear to be fairly complete, the authors report very little information on safety endpoints (i.e. drug-related side effects). In a trial where 22% of patients who completed the 4-week run-in/weed-out discontinued the study medications prematurely, this information would have been valuable.

3. Are the likely treatment benefits worth the potential harms and costs?

By the end of the study, 1350 (22%) of the patients had prematurely discontinued all study tablets. The overall proportion of discontinuation was similar in both active and placebo groups. The main reasons for discontinuation were participant's decision, cough, hypotension, and heart failure requiring treatment with an ACE inhibitor or diuretic. There were more discontinuations for cough and hypotension in the active treatment group. There is no mention as to whether patients tolerated single therapy better than combination therapy. Other safety data is not included in the publication.

For those patients who did tolerate the study medications, the therapeutic benefit appears to be associated with using combination therapy, as opposed to single agent therapy only. The cost of perindopril or indapamide is not significantly different than that of other ACE inhibitors or diuretics (e.g. hydrochlorothiazide) commonly used to treat hypertension post-stroke. However, the cost of diuretics is considerably less than that of ACE inhibitors. This may be an important consideration when looking at treating all post-stroke patients, both hypertensive and non-hypertensive.

Commentary

The PROGRESS study adds another piece of information to the growing literature on ACE inhibitors and diuretics for prevention of cerebrovascular events. What is striking about this particular study is that the results suggest that the indapamide was responsible for the benefit seen in the combination group. One would have expected a reduction in stroke risk in the perindopril group based on the observed drop

in blood pressure, however this was not the case. (1) Unfortunately, the study was not designed to determine if this benefit truly was the work of indapamide as there was no indapamide-alone group.

From previous studies, we know that the evidence for diuretics in stroke reduction is fairly consistent. In the Post-stroke Antihypertensive Treatment Study (PATS), indapamide 2.5 mg PO daily lowered blood pressure about 5/2 mm Hg and demonstrated a 29% relative reduction in stroke recurrence. (2) In the Systolic Hypertension in the Elderly Program (SHEP), treatment of isolated systolic hypertension with chlorthalidone 25 mg PO daily resulted in a 36% relative reduction in total stroke frequency. (3)

On the other hand, evidence for the use of ACE inhibitors has not been as consistent. The Captopril Prevention Project trial demonstrated that captopril lead to an increased risk for stroke compared to diuretics, b-blockers, or both. (4) In the HOPE study, ramipril 10 mg PO daily was associated with a 1.5% absolute reduction in stroke overall. (5) However, when examining the subgroups, it appears that the benefit was seen in patients without previous stroke/TIA, as ramipril provided no statistically significant benefit in patients with previous stroke/TIA.

Another interesting point is the heterogeneity between the combination and single therapy groups. Patients who received the benefit were younger, male, had higher baseline blood pressures, and were more likely to have coronary heart disease. One could argue that combining the results of these two very different patient populations should not be done, especially considering the confounding role that indapamide (which has previously shown efficacy in stroke reduction) may have played.

So where does all of this leave clinicians and patients? The authors suggest that treatment with perindopril and indapamide should be considered routinely for patients with a history of stroke or TIA, regardless of blood pressure. Overall, it appears that intensive blood pressure lowering, even in “normotensive” patients may reduce stroke risk. However, without a direct comparison of diuretic versus diuretic plus ACE inhibitor, we really can’t be certain that addition of an ACE inhibitor will substantially increase the benefit over a diuretic alone. Considering the cost of implementing combination therapy in all post-stroke patients, this information would be valuable to have.

In summary, PROGRESS suggests that all stroke patients, regardless of hypertensive status, should be initiated on a diuretic. Addition of an ACE inhibitor may be necessary to achieve blood pressure goals or if certain comorbid illnesses (e.g. diabetes) exist; however, when one considers all of the available ACE inhibitor evidence to date, these agents may not actually confer any additional benefit in stroke reduction as compared to a diuretic alone.

Author Competing Interests

None declared.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2002;11:201.

Once-Yearly Treatment For Osteoporosis: Is Zoledronic Acid Worth The Shot?

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Reviewer's profession/specialty: Pharmacist/PharmD student (University of Toronto)

Original Citation

Reid IR, Brown JP, Burckhardt P et al. Intravenous zoledronic acid in postmenopausal women with low bone mineral density. N Engl J Med 2002; 346: 653-61. [PubMed Citation](#)

Overall Study Question

This phase 2 randomized, multicentre, double blind, placebo-controlled trial was designed to determine the effects of 5 dosing regimens of intravenous zoledronic acid, the most potent bisphosphonate available to date, on bone mineral density (BMD) and bone turnover in postmenopausal women with low BMD.

This trial included 351 postmenopausal women, aged 45 to 80 years. The onset of menopause was defined as the date of oophorectomy if applicable, or 12 months after the cessation of menses in women over 50 years of age, and 18 months after the cessation in menses in women between 45 and 49 years of age. Women were eligible for this study if they had a BMD at the lumbar spine that was at least 2.0 standard deviations (SD) below the mean value for young adults (this corresponds to a T score lower than -2), and had no more than one vertebral fracture at screening.

Exclusion criteria were as follows: systemic estrogen treatment within the past 3 months; evidence of secondary osteoporosis (e.g. steroid-induced osteoporosis); clinical or laboratory evidence of hepatic or renal disease; disorders of the parathyroid or thyroid glands; a serum 25-hydroxyvitamin D concentration ≤ 15 ng/mL; a history of cancer; previous treatment with bisphosphonates or fluoride; or current therapy with any other drug known to affect the skeleton.

Patients were randomized to receive placebo or zoledronic acid. All patients received calcium supplementation (1 g/day). The duration of the study period was 12 months.

BMD of the lumbar spine, the non-dominant proximal femur and forearm, and the total body were measured by dual-energy-x-ray-absorptiometry (DEXA) at baseline, 6, 9, and 12 months. Biochemical

markers of bone turnover were also evaluated at baseline and every 3 months for most patients. Markers of bone formation included serum bone-specific alkaline phosphatase and serum osteocalcin. Markers of bone resorption included serum type I collagen C-telopeptide and urinary type I collagen cross-linked N-telopeptide. The primary study endpoint was BMD of the lumbar spine at 12 months.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Patients were randomized to receive one of the following: (1) placebo; (2) zoledronic acid 0.25 mg IV every 3 months; (3) zoledronic acid 0.5 mg IV every 3 months; (4) zoledronic acid 1 mg IV every 3 months; (5) zoledronic acid 2 mg IV every 6 months; (6) zoledronic acid 4 mg IV x 1 dose.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. This trial included 351 post-menopausal women. During the study, 35 patients withdrew (15 because of personal reasons; 14 withdrew due to adverse effects). Dropout rates appeared to be similar across all treatment arms. Thus, 316 women completed the study. Data were analyzed for 351 women according to the intention-to-treat principle.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. This was a double-blind trial. In order to maintain blinding, all women received an intravenous infusion of either zoledronic acid or placebo every 3 months. All infusions were 20 mL in volume and were infused over 5 minutes. Infusions were prepared at each center by a pharmacist who had no contact with the patients.

4. Were the groups similar at the start of the trial?

Yes. The groups appeared to be similar at baseline.

5. Aside from the experimental intervention, were the groups treated equally?

Yes. Study procedures appeared to be identical for both groups, with follow-up at 3, 6, 9 and 12 months. All patients received 1 gram elemental calcium PO daily.

What were the Results?

1. How large was the treatment effect?

For the primary endpoint, there was a progressive increase in BMD of the lumbar spine over 12 months that was similar for all zoledronic acid groups, with values that were significantly higher (4.3 to 5.1%) than placebo ($p < 0.001$).

BMD values for the femoral neck were 3.1 to 3.5% higher for zoledronic acid compared to placebo ($p < 0.001$). Distal radius BMD was significantly higher (0.8 to 1.6%) compared to placebo for most of the zoledronic acid groups ($p \leq 0.05$), with the exception of the 0.25 mg 4-dose regimen. Total body BMD was higher (0.9 to 1.3%) compared to placebo for most of the zoledronic acid groups ($p < 0.03$), with the exception of the 0.5 mg 4-dose regimen.

The authors reported that biochemical markers of bone resorption reached a nadir at 1 month with zoledronic acid treatment (median decreases of 65 to 83% in serum C-telopeptide and 50 to 69% in the urinary N-telopeptide: creatinine ratio), whereas there were no significant changes in the placebo group. However, given that most samples were obtained every 3 months, it is difficult to know the exact time to maximal suppression of biochemical markers. The decrease in markers of resorption tended to be dose-dependent. Suppression of biochemical markers of bone resorption was maintained at 12 months with zoledronic acid. All zoledronic acid groups had values for these markers that were significantly different from those in the placebo group ($p < 0.01$ for all comparisons), but there were no significant differences among the zoledronic acid groups. Biochemical markers of bone formation, such as serum osteocalcin and bone-specific alkaline phosphatase) showed no sharp decrease apparent at 1 month, but suppression persisted at 12 months with all doses ($p < 0.001$).

The authors also reported that during the study period there were no vertebral fractures, and 5 non-vertebral fractures in patients taking zoledronic acid, compared to 1 patient taking placebo.

2. How precise was the estimate of the treatment effect?

This trial was designed to detect a difference of at least 4% in the degree of change from baseline to 12 months in primary endpoint (lumbar spine BMD). The authors did not report confidence intervals for any of the study endpoints.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. The methodology of this trial was fair, and the results can be considered valid. The results can be applied to patients that would fit in to the inclusion criteria of this study. It is important to note that the patient population in this trial may be considered a low-risk population for fractures. Post-menopausal women were eligible for this study if they had a BMD at the lumbar spine that was at least 2.0 standard deviations (SD) below the mean value for

young adults (this corresponds to a T score lower than -2). This BMD classifies the patient as being osteopenic, while a T score lower than 2.5 confers a diagnosis of osteoporosis. (1-3)

2. Were all clinically important outcomes considered?

Ideally, it is desirable to look at the effects of treatment of the incidence of fractures, particularly hip fractures, which are associated with significant morbidity and mortality. (4) The investigators evaluated the impact of treatment on BMD, which may be considered an acceptable surrogate endpoint in this trial for several reasons. Firstly, the patients included in this trial were a low risk osteoporosis population who had a low baseline risk of fractures. Thus, the sample size or duration of follow-up would need to be increased in order to detect whether treatment would impact the fracture rate in this patient population. Secondly, there seems to be a good correlation between BMD and incidence of fractures based on existing data for bisphosphonates. (2,3) Assessing BMD of the lumbar spine is appropriate as a primary outcome measure since the lumbar spine is most useful for assessing therapeutic response since changes are of the earliest and greatest magnitude because of the high rate of remodeling.

Other endpoints that were evaluated in this trial include biochemical markers of bone turnover. These surrogate endpoints are of interest because they may be important predictors in determining response to therapy. (5) Clinically relevant adverse effects such as hypersensitivity and infusion site reactions, acute renal insufficiency and hypocalcemia were also considered in this trial.

3. Are the likely treatment benefits worth the potential harms and costs?

Acute renal insufficiency and hypocalcemia are two important short-term effects that have previously been reported with the administration of intravenous bisphosphonates. In this trial, while there were no episodes of acute renal insufficiency noted, mean serum calcium concentrations in the zoledronic acid groups declined significantly, by approximately 0.08 mmol/L between baseline and one month ($p < 0.05$ for all comparisons). From 3 months onwards, calcium concentrations were similar between the zoledronic acid and placebo groups.

In the past, there have been concerns about a potential negative impact of intravenous bisphosphonates on bone mineralization. Preliminary findings from a limited number of bone biopsy samples taken during this study indicated no change in cortical bone thickness, cancellous bone volume, trabecular thickness, separation or number, and no evidence of osteomalacia in patients receiving zoledronic acid. Further study is required in order to determine the impact of intravenous zoledronic acid on bone mineralization.

Mild myalgia, pain, nausea and fever also occurred more frequently in patients receiving zoledronic acid. The annual cost of zoledronic acid is estimated to be approximately \$600 CDN. Comparatively, the annual costs of etidronate, alendronate and risedronate are estimated to be approximately \$200, \$500-800, and \$750 CDN, respectively.

Commentary

Although zoledronic acid is currently only indicated for the treatment of hypercalcemia of malignancy in Canada, its use in osteoporosis is appealing since its high potency may allow use of smaller doses with extended dosing intervals, thus possibly leading to reduced adverse effects and improved patient compliance. This trial, sponsored and designed by the manufacturer of zoledronic acid, suggests that the drug may be potentially useful in the management of post-menopausal osteoporosis.

Some of the limitations of this study must be highlighted. Firstly, the women who participated in this trial did not necessarily meet the diagnostic criterion for osteoporosis, and in fact could be considered a low risk population for fractures. (1-3) As such, the authors used this as justification for the use of a placebo comparator arm. Secondly, this trial does not provide a direct comparison with oral bisphosphonates. And finally, even though the use of surrogate endpoints may have been acceptable in this trial, this study did not demonstrate the effect of zoledronic acid on the most clinically relevant endpoint, namely fracture rates.

The effects of zoledronic acid on BMD noted in this trial are consistent with what has been observed with oral bisphosphonates in previous trials. When given either daily or intermittently (e.g. once-weekly alendronate), oral bisphosphonates tend to increase BMD of the lumbar spine by approximately 3 to 6% in one year, with less of an effect on hip BMD. Thus, based on an indirect comparison, the effects of zoledronic acid on BMD may be considered comparable to that of oral bisphosphonates^{2,3}.

In general, zoledronic acid appeared to be well-tolerated in this trial, with the most common adverse effects being decreased calcium concentrations, myalgia and pyrexia associated with its administration. Thus, zoledronic acid may be an attractive option for treating osteoporosis as once-yearly dosing has the potential to dramatically increase patient compliance and possibly minimize the risk of adverse effects compared to current oral bisphosphonate therapy. While the annual cost of zoledronic acid seems comparable to that of other bisphosphonates on the market, data on the cost-effectiveness of this intervention is needed. Thus, one may consider zoledronic acid to be “worth the shot” in certain patients, for example, those who have not tolerated daily or intermittent dosing of oral bisphosphonates without contraindications to therapy. Nevertheless, the long-term efficacy and safety of zoledronic acid in post-menopausal women with low BMD are unknown, and its role in therapy needs to be further defined.

Author Competing Interests

None declared.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2002;11:202.

Low Dose Corticosteroids to Reduce Mortality in Patients with Septic Shock: Selective Benefit?

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Original Citation

Citation

Annane D, Sebille V, Charpentier C, Bollaert PE, Francois B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troche G, Chaumet-Riffaut P, Bellissant E. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002;288:862-871. [PubMed Citation](#)

Overall Study Question

This trial was a prospective, randomized, placebo-controlled study conducted in 19 intensive care units in France from September 1995 to March 1999. The study was designed to assess if endocrine replacement therapy with hydrocortisone and fludrocortisone could improve 28-day survival in patients with septic shock and relative adrenal insufficiency.

Hospitalized adult patients were included if they had clinical characteristics of the systemic inflammatory response syndrome (SIRS) with suspected or documented infection and signs of hypoperfusion and organ dysfunction and met all 7 of the following inclusion criteria: (1) temperature < 35.6°C or > 38.3°C; (2) heart rate > 90bpm; (3) presence of polymorphonuclear leukocytes or a positive gram stain or culture of a normally sterile body fluid, or clinical focus of infection, or a wound with purulent discharge, or other evidence of systemic infection; (4) systolic blood pressure < 90 mmHg despite 1 hour of adequate fluid replacement, or dopamine > 5 mcg/kg/min, or any treatment with epinephrine or norepinephrine; (5) urinary output < 0.5 mL/kg/h, or PaO₂:FiO₂ ratio < 280; (6) mechanical ventilation; and (7) arterial lactate > 2 mmol/L. Patients initially had to be enrolled within 3 hours of the onset of shock, however a protocol amendment on July 18, 1996 removed arterial lactate as a criterion, and the enrolment window was extended to within 8 hours of the onset of shock.

Patients were excluded if they were pregnant, had evidence of acute myocardial infarction or pulmonary embolism, advanced cancer or AIDS infection, and contraindications or formal need for corticosteroids. A protocol amendment on June 19, 1997 also excluded patients receiving etomidate within 6 hours of randomization.

Patients were randomized to hydrocortisone 50mg IV every 6 hours plus 0.5mg of fludrocortisone via a nasogastric (NG) tube or matching placebos for 7 days. At inclusion, patients received a short corticotropin (ACTH) test using a 250mcg IV bolus of tetracosactrin, and were subdivided into “responders” if their 30 or 60 minute cortisol response was > 9 mcg/dL (250 nmol/L), or “nonresponders” if the cortisol response was ≤ 9 mcg/dL (250 nmol/L).

The primary outcome was stated as the 28-day survival distribution from randomization in the subgroup of patients who were ACTH stimulation test “nonresponders”.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Concealed randomization was centrally performed using a computer-generated random number table, and participants were stratified into blocks of four patients. The randomization process was not stratified based on whether patients were “nonresponders” or “responders” to the ACTH stimulation test because the results of the test were not available until after the patient received the study drug. Thus, although patients did have an equal chance of receiving placebo or active treatment in the overall cohort, this was not the case within the subgroups analyzed as “nonresponders” or “responders”.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. During a 42-month period, 1,326 patients were screened, and 300 (23%) were enrolled. A screening log was kept and a study flow chart was provided that accounted for all of the patients screened and enrolled in the trial. None of the patients discontinued treatment or were lost to follow up. The primary outcome was analyzed using an intention-to-treat strategy.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. The randomization schedule was concealed, identical placebos were used, and all patients, medical, nursing, and pharmacy staff were blinded to the treatment allocation throughout the study period.

4. Were the groups similar at the start of the trial?

Yes. Overall, patients in the placebo and active treatment groups had similar baseline demographic, clinical, and prognostic characteristics. Of the entire cohort, 18% were “responders” to a 250 mcg ACTH stimulation test with a good prognosis based on their adrenal response profile. The remaining 82% of patients were “nonresponders”, with 73% classified as having an intermediate prognosis and 9% classified as having a poor prognosis based on their

adrenal response profile.

Since the randomization process was not stratified by response to the ACTH stimulation test, baseline clinical or prognostic factors may not have been equally distributed between the placebo and active treatment groups within the “nonresponders” subgroup. In this subgroup, 5% more patients in the placebo arm had emergency surgery, and 6% more had a poor prognosis based on the baseline short corticotrophin test. Four percent more patients in the placebo arm received what was determined to be appropriate antibiotics.

5. Aside from the experimental intervention, were the groups treated equally?

Yes. There was limited information concerning the co-interventions used and whether they were mandated by the investigators. Since the randomization process was not stratified by response to the ACTH stimulation test, and the primary analysis was of a subgroup, we cannot assume that known or unknown prognostic factors or co-interventions were balanced between the placebo and active treatment groups within the “nonresponders” subgroup. Nonetheless, the amount of fluid administered, dosage of vasopressors, time to vasopressor treatment, and ventilatory support appeared similar between the placebo and active treatment arms within the “nonresponders” subgroup.

What were the Results?

1. How large was the treatment effect?

In the primary analysis of the “nonresponders” subgroup, the 28-d mortality was 53% in the corticosteroid group, and 63% in the placebo group (unadjusted ARR = 10.8% (-1.9% to 23.6%) calculated from a 2x2 table, $p=NS$; reported RR = 83% (66% to 104%), $p=NS$). Using a Cox proportional hazards model to adjust for differences between the groups in prognostic factors, the adjusted analyses showed a statistically significant 28-day mortality benefit (OR = 0.54 (0.31 to 0.97), ($p=0.04$), NNT = 7 (4 to 140; my calculation); HR = 0.67 (0.47 to 0.95), ($p=0.02$), NNT = 7 (4 to 56)). The reported NNT for the 28-day mortality endpoint was 7 (4 to 49).

In the entire cohort, the 28-day mortality was 55% in the corticosteroid group and 61% in the placebo group (unadjusted ARR = 6.4% (-4.8% to 17.6%) calculated from a 2x2 table, $p=NS$; adjusted OR = 0.65 (0.39 to 1.07), $p=NS$). The adjusted hazard ratio was also statistically significant (HR = 0.71 (0.53 to 0.97), $p=0.03$, NNT = 8 (5 to 90, my calculation)). The reported NNT for the 28-day mortality endpoint was 8 (5 to 81).

The benefit for the entire cohort was driven by the effect in the “nonresponders” subgroup, which comprised the majority of the patients in the trial. There was no mortality benefit in the “responder” group (adjusted OR = 0.97 (0.32 to 2.99)) and the widely skewed confidence intervals failed to rule out a clinically important harm from corticosteroids in this subgroup.

In both the “nonresponder” subgroup and the entire cohort, patients receiving corticosteroids had a shorter median time to withdrawal of vasopressor support. The unadjusted ARR for remaining on vasopressors during the 28-day period was 17.0% (4.3% to 29.8%) (NNT = 6 (3 to 23) in the “nonresponder” subgroup; ARR = 12.4% (1.1% to 23.6%), NNT = 8 (4 to 91) in the entire cohort).

There were no significant differences between the corticosteroid and placebo groups in the incidence of adverse effects possibly related to corticosteroids or vasopressors in either group at 21% vs. 22% and 3% vs. 2% respectively. No patients in either group discontinued treatment due to adverse effects.

2. How precise was the estimate of the treatment effect?

For the primary outcome of 28-day mortality in the “nonresponders” to the ACTH stimulation test, the ARR for the raw analysis crossed zero, and was not statistically significant. The confidence intervals (CI) are definitely skewed towards benefit in the treatment group however, and the lack of statistical significance from the raw analysis may be due to a lack of statistical power. The 95% CI for the adjusted analyses using the OR and HR were statistically significant as they did not cross zero, but were quite wide. Interestingly, the authors report the results of the analysis with the narrowest 95% CI in the abstract. Based on the article the author's reference for the NNT calculation, it appears that their calculations of the NNT and their 95% CI are incorrect.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. In a very select proportion of critically-ill septic shock patients who are “nonresponders” to a 250 mcg ACTH stimulation test, the combination of hydrocortisone 50 mg IV q6h and fludrocortisone 0.5mg NG daily given within 8 hours of the onset of septic shock may shorten the time to withdrawal of vasopressor support and may reduce 28-day overall mortality.

2. Were all clinically important outcomes considered?

Although this trial was underpowered to show a difference in hospital and 1-year mortality, these endpoints are reported, and there was a strong trend toward improved survival in both the “nonresponders” and the entire cohort. Although adverse effects were prospectively evaluated, it would be very difficult to determine which adverse effects were attributable to the study drug, and the utilization of a validated adverse drug reaction scoring system would have been beneficial. Furthermore, the incidence of hyperglycemia, which can adversely affect outcome, was not reported in the trial.

3. Are the likely treatment benefits worth the potential harms and costs?

Although corticosteroid therapy shortened the time to withdrawal of vasopressor support, this is a surrogate endpoint and may not be of clinical benefit in patients tolerating vasopressor therapy. However, this is the first trial to show a reduction in 28-day overall mortality in a subgroup of ACTH stimulation test “nonresponders”, with no detectable increase in adverse effects or significant drug acquisition costs associated with therapy. The safety of corticosteroid use in ACTH stimulation test “responders” needs to be confirmed in a larger trial.

Commentary

Although many specific anti-sepsis therapies have been studied over the past four decades, until recently, no therapy has reduced overall mortality in patients with severe sepsis or septic shock. Activated protein C is indicated in the U.S. for the reduction of mortality in adult patients with severe sepsis (i.e. sepsis associated with acute organ dysfunction) who have a high risk of death (as determined by APACHE II score). Although the NNT to prevent one death at 28 days with activated protein C is 15 (9 to 45), there is a strong trend towards increased serious bleeding (3.5% vs. 2.0%, $p=0.06$), and the acquisition cost based on a 4-day course of therapy for a 70-kg patient is ~\$6800 US. (1) More recently, intensive insulin therapy for aggressive control of blood glucose in mechanically-ventilated surgical ICU patients has also shown a reduction in 12-month mortality (4.6% vs. 8.0%), ARR = 3.5% (1.1% to 5.9%), NNT = 29 (17 to 91). (2)

Two meta-analyses of short-course, high-dose corticosteroids failed to show a benefit on overall mortality in septic shock, and a strong trend towards increasing mortality. (3,4) Two small published randomized, controlled trials (RCT) and one unpublished abstract of a small RCT in patients with septic shock have shown that early or late treatment with hydrocortisone 300mg/d given either as intermittent bolus doses or by continuous infusion for at least 5 days improves the blood pressure response to vasopressors and shortens the time to withdrawal of vasopressor support. (5-7)

The current trial confirms the hemodynamic benefits of corticosteroids in a very select proportion of critically-ill patients, and is the first corticosteroid trial to show a reduction in 28-day overall mortality. The results of this trial suggest that a 250mcg IV ACTH stimulation test should be performed within 8 hours of the onset of septic shock in all patients meeting the inclusion criteria from this trial. This should be followed immediately by the administration of hydrocortisone and fludrocortisone. The results of the ACTH stimulation test will identify the subgroup of “nonresponders” who may achieve a survival benefit from continuing this combination therapy for 7 days.

There are concerns over the non-stratified randomization strategy in this study, and the primary analysis was of a subgroup of “nonresponders” in which there may have been differences in baseline characteristics, prognostic variables or treatment factors between the patients who received corticosteroids and those who received a placebo. Larger, appropriately randomized, adequately powered studies are required to confirm the efficacy of corticosteroid replacement in all septic shock patients and ACTH stimulation test “nonresponders”, and to rule out a potentially detrimental effect of routine corticosteroid treatment in ACTH stimulation test “responders”.

Author Competing Interests

None declared.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;11:400.

Faculty of Pharmaceutical Sciences, University of British Columbia Alan C. Hayman Summer Student Research Competition 2002

Partial Proceedings from the Faculty of Pharmaceutical Sciences Summer Student Research Program Poster Competition

Abstracts

PHARMACOKINETICS OF MYCOPHENOLATE IN THE EARLY PERIOD FOLLOWING LUNG AND HEART TRANSPLANTATION

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Anthony Chau, Ric M. Procyshyn, Willough Jenkins, Patricia Fortin

PHARMACOKINETICS OF MYCOPHENOLATE IN THE EARLY PERIOD FOLLOWING LUNG AND HEART TRANSPLANTATION

Leanne Kwan, Nilufar Partovi, Diane Decarie, Robert D. Levy, Guy Fradet, Andrew P. Ignaszewski, Mary H.H. Ensom.
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Purpose: The purpose of this pilot study was to evaluate the pharmacokinetics of mycophenolic acid (MPA) at 3 different times in the early period following lung or heart transplantation.

Methods: Nine patients were entered into this open-label study. Upon administration of a steady-state morning mycophenolate mofetil (MMF) dose, blood samples were collected at 0, 20, 40, 60, and 90 minutes and at 2, 4, 6, 8, 10, and 12 hours post-dose, at 3 different times in the early post-transplant period (targeted at post-transplant days 5-7, 20-40, and 60-80, respectively, and denoted as Sampling Periods 1, 2, and 3). Total MPA concentrations were measured by a validated high performance liquid chromatography (HPLC) method with ultraviolet detection and followed by ultrafiltration of pooled samples for free MPA concentrations. Pharmacokinetic parameters were calculated by traditional noncompartmental methods.

Results: Patient characteristics included: 7 males and 2 females; 5 lung and 4 heart transplant recipients; mean ($\pm$ SD) age of 53 $\pm$ 11 yr; and weight of 77 $\pm$ 14 kg. All patients were on prednisone and cyclosporine (with the exception of 2 patients on tacrolimus during Sampling Periods 2 and 3). Sampling Periods 1, 2, and 3 occurred on post-transplant days 15 $\pm$ 13, 56 $\pm$ 33, and 125 $\pm$ 73, respectively. Mean ($\pm$ SD) parameters are as follows:

Sampling Period	A LB g/L	SrCr μ mol/L	Dosage		Cmax μ g/mL	DN Cmax μ g/mL	T max h	Cmin μ g/mL	AUC μ g*h/ mL	DN AUC μ g*h/mL	f %	free AUC μ g*h/ mL
			mg/day	mg/kg/ day								
1	32* (9)	129 (44)	2444 (527)	34.1 (11.4)	10.25 (7.86)	9.21 (7.99)	3.2 (4.01)	0.25 (0.52)	39.95 (44.86)	36.74 (44.81)	7.1 (3.6)	4.03 (6.62)
2	34 (5)	126 (53)	2500 (500)	36.8 (13.7)	8.83 (5.86)	7.18 (4.45)	0.8 (0.6)	0.34 (0.53)	25.24 (25.68)	20.72 (18.27)	4.3 (2.1)	1.14 (1.06)
3	37* (5)	134 (77)	2389 (486)	34.2 (10.9)	12.51 (9.53)	10.37 (7.74)	1.5 (1.2)	0.94 (1.63)	43.96 (38.67)	35.50 (27.17)	5.0 (2.9)	2.30 (3.10)

Conclusions: This is the first study to systematically evaluate MPA pharmacokinetics in thoracic transplant recipients at 3 different time points during the early post-transplant period. Wide inter-patient variability in MPA pharmacokinetics was observed, thus emphasizing the need to individualize dosing of MMF and to further evaluate important pharmacokinetic/pharmacodynamic parameters and endpoints that impact on clinical outcomes. Further studies involving more patients and pharmacodynamic outcomes are underway to help identify optimal MMF strategies. Acknowledgements: BC Health Research Foundation/ BC Transplant Foundation; BC Research Institute for Children's & Women's Health; LK was supported by a CIHR Health Professional Student Research Award.

PSYCHIATRIC RATING SCALES, SIDE EFFECTS, COMPLIANCE AND OTHER ASSESSMENTS OF PSYCHIATRIC INPATIENTS: FINDING THE CORRELATION

Kaleena Patel, Ric M. Procyshyn, Deborah Thompson. Riverview Hospital, Port Coquitlam, British Columbia, Canada, Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, British Columbia, Canada

Objective: To determine if there is a correlation between the various psychiatric rating scale scores and clinical pharmacist's notes, medication side effects and compliance of psychiatric inpatients.

Methods: This retrospective study involved the review of clinical pharmacists' notes of patients on their admission to the Refractory Psychosis Unit of Riverview Hospital, British Columbia. Psychiatric rating scales included the Drug Attitude Inventory to measure patient compliance, and the ESRS to identify movement disorders. The therapeutic category and total number of patient's medications was recorded. Caffeine intake and nicotine use were also included.

An analysis of the numerical data was performed, comparing one set of measurements against another to reveal correlations between any of these measurements.

Results: Data comparison identified two statistically significant correlations were found: patients who smoked tended to use more anticholinergic medications, and scored lower on the DAI. All other data was relatively similar between smoking and nonsmoking patients.

Conclusion: Two correlations may exist, indicated by higher anticholinergic medication use and lower DAI scores in smoking patients. There may be several possible explanations for these trends, ranging from the chemical effects of nicotine at receptor sites to the inherent characteristics of addiction and addictive behaviour in these patients. Further research into the type and frequency of anticholinergic drug use, the accompanying side effects, patient-medication compliance, and the effects of smoking on all of these factors is required.

MEDICATION SPECIFIC PREDICTORS OF ADHERENCE WITH CARDIOVASCULAR REGIMENS

Ivana Dojcinovic and Stephen Shalansky. Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, British Columbia, Canada.

Purpose: The goal of this study was to identify medication specific predictors of adherence with cardiovascular regimens (e.g. frequency, medication class, etc.).

Methods: A survey was administered to 458 subjects who had taken a lipid lowering medication or an angiotensin converting enzyme (ACE) inhibitor for at least 3 months. Information was collected on non-prescription drug use, demographics, adverse effects, and use of adherence aids. Prescription medication use data over the previous 14 months was obtained for each subject from the Pharmanet, British Columbia prescription claims database. Adherence for each prescription medication was calculated based on prescription fill dates and number of days supplied. Univariate and multivariate analyses were used to identify medication specific predictors of adherence (<80%) with cardiovascular medications while controlling for individual patient characteristics.

Results: Of the 1543 drugs that were taken by 458 patients, 209 (13.5%) drugs were taken less than 80% of the time. Fifty-eight (12.7%) subjects were categorized as non-adherent. Medication class did not appear to independently predict adherence; however, adherence with cardiac glycosides was slightly higher than for other medication classes ($95.3\% \pm 9.2\%$ vs. $91.8\% \pm 14.1\%$, $P < 0.001$). The majority of medications were taken once (74.1%) or twice daily (21.3%). Controlling for the effects of alternative medicine use, number of over-the-counter medications consumed, number of regular prescription medication consumed, use of adherence aids, living alone and clinic participation, adherence was less likely for drugs taken more often than once daily (OR 0.67, 95% CI 0.48-0.93, $P = 0.02$). However, the clinical importance of this is questionable since there was little difference in the percent adherence between drugs taken = once per day, and those taken > once per day ($92.5\% \pm 13.7\%$ vs. $91.1\% \pm 14.1\%$, $P = 0.09$). The use of adherence aids also appeared to be an independent predictor of adherence with individual medications (OR 1.48, 95% CI 1.06-2.05, $P = 0.02$).

Conclusions: Within this study cohort, once daily dosing and use of adherence aids were found to be independent medication-specific predictors of adherence. However, though once daily dosing appears to have a statistically significant impact on adherence, the clinical impact is likely negligible.

ESTABLISHING A LIMITED SAMPLING STRATEGY FOR CYCLOSPORINE (NEORAL™) IN PEDIATRIC RENAL TRANSPLANT PATIENTS

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Purpose: In pediatric renal transplant patients, 1) to define the optimal limited sampling strategy (LSS) for cyclosporine (CSA) (Neoral®) monitoring and to test its predictive performance, and 2) to characterize the pharmacokinetic parameters of Neoral®.

Methods: In Phase I, 11 pediatric renal transplant patients were entered into the study, following written informed consent. Upon administration of a steady-state morning Neoral® dose, blood samples were collected at 0, 0.5, 1, 2, 4, 6, and 8 hours post-dose. The whole blood samples were analyzed for CSA by fluorescence polarization immunoassay using a specific monoclonal antibody kit. Pharmacokinetic parameters were determined via non-compartmental analysis using WinNonlin® software. LSSs were determined by multiple regression analysis with forward stepwise elimination using Statistica® software. In Phase II, 16 patients underwent regular clinical monitoring of Neoral® and had blood collected and analyzed according to the above procedures. These data were used to test the predictive

performance [measured by the coefficient of determination (r^2), bias, and precision] of LSSs developed in Phase I. **Results:** Data from Phase I patients were used to derive the following LSSs; the predictive performance of these equations, as tested in Phase II patients, is depicted below:

Area-under-the-curve (AUC) Equations ($\mu\text{g}\cdot\text{hr}/\text{L}$)	r^2	Bias	Precision
$\text{AUC} = 6.98C_2 - 964.51$	0.84	0.21	0.32
$\text{AUC} = 1.02C_1 + 5.58C_2 - 830.94$	0.89	0.02	0.17
$\text{AUC} = 3.18C_0 + 5.69C_2 - 535.20$	0.83	0.15	0.23
$\text{AUC} = 1.14C_{0.5} + 6.24C_2 - 860.99$	0.84	0.15	0.24

For Phase I patients, mean $\pm$ SD AUC_{0-t} was 4660 $\pm$ 1849 mg $\cdot$ hr/L, C_{max} was 1060 $\pm$ 452 mg/L, C_{min} was 164 $\pm$ 101 mg/L, T_{max} was 1.1 $\pm$ 0.5 hours, and half-life was 5.0 $\pm$ 1.8 hours.

Conclusions: The optimal and most clinically feasible LSS for pediatric renal transplant recipients 1) requiring one blood sample is $\text{AUC} = 6.98C_2 - 964.51$; 2) requiring two blood samples is $\text{AUC} = 1.02C_1 + 5.58C_2 - 830.94$. This is based on patient wait time, number of blood samples required, coefficient of determination, bias, and precision. These are preliminary results as the final target for this study is n=25 for Phase I. Final study findings will be incorporated directly into clinical practice.

Acknowledgements: Elisa-Marie Babor, Dr. James Carter, Dr. Morrison Hurley, Dr. Colin White, Novartis Pharmaceuticals Canada Inc., and the BC Research Institute for Children's and Women's Health 2002 Summer Students' Research Program.

EVALUATING THE IMPLEMENTATION OF A COLLABORATIVE PHARMACIST RESEARCH NETWORK

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Purpose: To evaluate the implementation of a Collaborative Pharmacist Research Network (CPRxN) during its first year of operation, and to identify facilitators and barriers to the adoption and participation in the network's first study, which examined the effectiveness of bupropion for smoking cessation in 200 patients over a one-year period.

Methods: A survey based on Roger's Diffusion of Innovations Theory, and Roberts-Gray's Systems Model of the Implementation Phase of Innovation and Planned Change, was developed and mailed to the 149 network pharmacists from 50 community pharmacies throughout British Columbia. The survey contained questions that measured the innovation characteristics of the CPRxN and of the bupropion study. To improve response rates, a phone call was made to each pharmacy prior to the survey mailing and 2 weeks after the survey was sent. In addition, pharmacists were permitted to complete the survey anonymously and a \$10 cash honorarium was provided.

Results: Overall response rate was 75.9%, with 102 of 149 network pharmacists submitting completed surveys and an additional 11 pharmacists returning their surveys uncompleted with the \$10 honorarium. Of the completed surveys, 82.4% of respective pharmacists participated in the bupropion study (i.e., recruited at least one patient). Major motivating factors for pharmacist participation included the opportunity to participate in research, interest in the use of bupropion for smoking cessation, and the desire to improve pharmacy practice. However, 91.7% of pharmacists experienced at least one problem with the bupropion study in regards to its complexity and compatibility with pharmacy procedures. Major barriers included insufficient staffing at pharmacies, low priority placed for the bupropion study, inability to incorporate CPRxN duties into pharmacy practice, and being discouraged by a poor initial response from eligible patients. In addition, 32.8% of respective pharmacists believed the honorarium for patient

enrollment should be at least double that used for the bupropion study. The lack of new prescriptions for bupropion as a smoking cessation aid also made patient enrollment difficult. Furthermore, respondents identified team building, training, monitoring, and funding as areas where additional support could help in future studies.

Conclusions: The barriers to enrolling patients in the bupropion study stemmed mainly from the complexity and compatibility of the expected CPRxN duties. While some barriers are project-specific and out of the control of researchers, such as the decreasing number of bupropion prescriptions since 2000, others were related to CPRxN operation and can be managed by increased implementation support.

Acknowledgements: Funding provided by the BC Medical Services Foundation.

STUDENT DATA ANALYSIS OF A CROSS-DISCIPLINARY, CASE-BASED PROBLEM USING THE WEB-BASED LEARNING CENTRE IN A LARGE PHARMACEUTICS CLASS

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Background: An online, cross-disciplinary case-based problem was created and implemented during the 2001-2002 academic year. The problem was implemented in Pharmacy 311 (Drug Delivery Systems I) using the Web-Based Learning Centre as the delivery platform. Student feedback data was collected and analyzed to evaluate the effectiveness of this learning activity.

Methods: Following the four-week implementation of the problem, an online student survey was administered to the students. The survey included 26 multiple-choice questions and 3 open-ended questions. The multiple-choice questions utilized the Likert scale to quantify student opinions. All multiple-choice questions were analyzed for reliability using the Wilcoxin signed-rank test with an alpha level of 0.05. Chi-square contingency analysis was conducted on 9 pairs of survey questions in an attempt to establish correlation among student responses.

Results: A total of 125 students responded to the survey for a 94 percent response rate. The overall rating of the online problem ranged from 1 (poor) to 5 (excellent), with an average rating of 2.18. The overall rating for the learning activity was "fair". Nine pairs of correlation results were summarized as follows:

Major correlation				
Question #		Question #		p-value
26	Overall rating	03	Comfort in contributing online	<0.0001
		04	Depth of understanding	0.0003
		05	Teaching support	0.0013
		20	Inadequate time	<0.0001
		22	Having student answer all questions	0.0004
04	Depth of learning	20	Inadequate time	<0.0001
		10	Teaching support	0.2974
26	Overall rating	21	Student previous knowledge	0.0577
		06	Technical support	0.1242

Discussion: Students preferred to work on the online problem earlier during the term, and to have more time to research the guiding questions. Tutor support was perceived to be insufficient, suggesting that student learning

environment had not been optimized. Students complimented the flexibility and accessibility of the online problem. However, they also commented that online tutorial sessions are inefficient compared to face-to-face tutorial sessions. Furthermore, students felt that the depth of understanding of materials was not as deep as the face-to-face mode of delivery. This is contradictory to established literature.

Conclusion: An online, cross-disciplinary case-based problem was created and implemented in a large pharmaceuticals class. This new learning activity has the potential to enhance student cross-disciplinary thinking. Feedback data showed that online delivery of tutorial problems using the Web-Based Learning Centre is feasible. While students rated the online problem as "fair", Likert-scale data as well as written comments provided useful information for future implementation.

THE IMPACT OF COMPLEMENTARY AND ALTERNATIVE MEDICINE USE ON WARFARIN-RELATED ADVERSE OUTCOMES

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Purpose: The purpose of this study was to identify the prevalence of complementary and alternative medicine (CAM) use and its associated adverse outcomes (INR ≥ 4 or bleed) amongst a cohort of patients taking warfarin. In addition, exposure patterns to prescription medications, over-the-counter medications, vitamins and supplements were also identified.

Methods: Patients taking warfarin were identified through a review of pharmacy, cardiac rehabilitation clinic, anticoagulation clinic, and atrial fibrillation clinic records. Those patients consenting to participate were administered a cross-sectional standardized survey. Patients were queried as to their daily dose of warfarin, information regarding minor bleeding episodes, acute illness, alcohol consumption, hospitalization, and prescription and OTC drug use. Patients were also questioned regarding vitamin K-containing food consumption and CAM use. British Columbia's provincial prescription database (Pharmanet) was accessed, with patients' consent, providing information on prescription medication used for the three month period prior to the survey date. Patient INR values were obtained from medical laboratories when such data were available.

Results: The survey was completed by 156 patients, 71 (46%) of whom reported CAM use over the month prior to survey including 51 (33%) who had used at least one CAM reported to potentially increase the risk of bleeding or an INR outside of the therapeutic range. The most common potentially interacting CAMs were vitamin E (26%), garlic (10%), chamomile (6%) and coenzyme Q10 (5%). Sixty-nine patients (44%) reported bleeding events in the past month. Of the 146 patients for whom INR results were available, 19 (12%) had INRs = 4 and 52 (33%) had INR < 2 during the month prior to survey. Comparing patients who did and did not report the use of a CAMs that could potentially increase the risk an elevated INRs, there was an unexpected trend towards CAM users having lower incidence of an INR > 4.0 (16% versus 5% respectively, $P=0.06$). Comparing patients who did and did not use a CAM that could increase the risk of bleeding through anti-platelet effects, there was a similar trend towards CAM users being less likely to report bleeding events over the past month (48% versus 38% respectively, $p=0.22$), although the difference was not statistically significant for either comparison.

Conclusions: While the use of potentially interacting CAM was common amongst this cohort of warfarin patients, it did not appear to increase the risk of bleeding or having an elevated INR.

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PHYSICIAN DISPENSING OF NON-PRESCRIBED EMERGENCY CONTRACEPTIVE PILLS IN WOMEN IN BRITISH COLUMBIA

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Purpose: Emergency Contraceptive Pills (ECPs) are accessed through various sources in British Columbia, one of which is physicians. While physician prescribing of ECP is well recorded, "out-of-cupboard" ECP provision has not been well documented. However, out-of-cupboard provision has been estimated to be as high as 35% of the total number of ECP treatments distributed throughout BC. The purpose of this study was to quantify the "out-of-cupboard" dispensing from GP offices/clinics and to identify the prescribing and dispensing patterns of ECP by GPs.

Methods: The College of Physicians & Surgeons registry database was obtained. All apparent GPs were selected, then stratified by health region and randomized. Calculations performed in a prior pilot study determined the sample size for a full study. A 10% sample of registered GPs (373 physicians) was extracted from the database and the physicians

were invited to participate in the study. Physician offices were initially contacted by telephone and advised that a cover letter and one-page survey would be faxed. After completing the 10-item survey, the physician was requested to fax the document back to the research group. Non-responders were contacted by telephone twice, at a 2-week interval. Surveys were mailed to physicians without facsimile access.

Results: The response rate was 46% (173 completed surveys evaluated.) Respondents were 68% male, 60% were in group practices, and 68% were full-time physicians. In the previous 12 months, 68% of respondents provided ECPs without a prescription. During this period, respondents provided ECPs a mean of 25.6 times (range 1-260.) Ovral® was the ECP agent most often distributed by physicians, both through written prescriptions (83%) and out-of-cupboard sources (99%). Plan B™ was most often prescribed by 25% of respondents and most often provided by 7%. GPs in BC provided 4.00 ± 0.36 tablets per non-prescribed ECP treatment. Extrapolation of the data suggests that out-of-cupboard ECP provision is projected to be more than 196,000 Ovral® tablets per year. This represents a substantial proportion of Ovral® sales not previously captured by PharmNet, Planned Parenthood, and youth clinic data. Of physicians who provided out-of-cupboard ECPs, 15% reported providing them to patients for future use and 66% provided antiemetic tablets with the ECP treatment.

Conclusions: Out-of-cupboard ECP provision from physician offices is a substantial source of ECP distribution, which contributes considerably to the impact of ECP treatments on pregnancy and abortion rates in BC.

Acknowledgements: This study was funded by BC Ministry of Health Planning, BC Women's Hospital and Health Centre, and an AFPC/Apotex PACE Studentship.

ANALYZING THE PREVALENCE AND OUTCOME OF PHARMACEUTICAL INDUSTRY SPONSORED CLINICAL STUDIES INVOLVING RISPERIDONE OR OLANZAPINE (AN INTERIM ANALYSIS)

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Purpose: The purpose of this study is two-fold: 1, To investigate the prevalence of sponsorship in psychiatric literature involving two atypical antipsychotics: risperidone and olanzapine. 2. To determine the outcomes of clinical trials that are sponsored by pharmaceutical industry.

Methods: Both antipsychotics were initially searched by subject and keyword between the years 1990 and 2002. Following this, "schizophrenia and disorders with psychotic features" was exploded in Medline. This search was next limited to the different types of clinical trials (i.e., phase I, II, III, IV, controlled, multicenter and randomized). A final limit by Human and English language was then performed. All studies found within the search were compiled. Excluded were review articles, letters and meta-analyses. Data collected included the following parameters: Disclosure of any financial support, author(s) employed by the industry, comparator drug(s) within the trial, sample size, blinding, placebo controlled, and outcome (if the study was sponsored).

Results: The literature search captured a total of 347 published journal articles of which 198 met the inclusion criteria for our study. Ninety-five (48%) of these studies were Industry sponsored (56 by Eli Lilly and 39 by Janssen). Regarding authorship, industry-employed authors was significantly higher for the studies funded by Eli Lilly compared to Janssen (76.8% vs. 23.1% respectively, $p < 0.05$). However, significantly more of the Eli Lilly sponsored studies compared their antipsychotic (olanzapine) to at least one other atypical antipsychotic (28.6 vs. 10.3% for Janssen sponsored studies, $p < 0.05$). Overall, no significant difference was noted for positive outcomes reported in the industry sponsored studies (91.1% vs. 79.5 for Eli Lilly and Janssen sponsored studies respectively). What's more, no negative results were reported in any of the funded studies. The major difference between the non sponsored studies and the industry sponsored studies is that the latter were more likely to be blinded and placebo controlled.

Conclusions: Almost 50% of published clinical trials involving olanzapine or risperidone have been funded by their respective manufacturer. Furthermore, the reported outcomes of the sponsored studies are highly in favor of their respective product.

Acknowledgements: Funding for this project was provided by the Canadian Institute of Health Research.

Research Abstracts

The Journal of Informed Pharmacotherapy 2002;11:400.

Appropriateness, Time to Treatment, and Medication Errors with Reteplase and Alteplase for Acute Myocardial Infarction

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 8, 2002.

Objectives

In the medical management of acute myocardial infarction (AMI), delays in door-to-needle time and medication errors during thrombolytic administration can have a negative impact on patient outcome. The aim of this study is to evaluate and compare the use of alteplase and reteplase for AMI at Lion's Gate Hospital (LGH) with respect to appropriateness of choice of therapy over streptokinase, door-to-needle time, medication errors, and efficacy and toxicity.

Setting

A Canadian community hospital.

Design

A retrospective chart review of patients admitted to LGH emergency department from August 1, 2000 to April 30, 2002 with a primary diagnosis of AMI was performed.

Results

A total of 52 patients receiving either alteplase (n=30) or reteplase (n=22) were included in the study. The choice of either fibrinolytic agent studied instead of streptokinase was inappropriate in 17 (33%) of the cases reviewed. Median door-to-needle times were 20 minutes with reteplase and 30 minutes with alteplase; 82% of reteplase patients and 53% of alteplase patients were treated within the 30 minute target. This was driven mostly by a shorter data-to-drug time. There appeared to be a fewer number of medication time errors with reteplase than with alteplase (9% vs. 27%), as well as a smaller mean magnitude of time errors (25% vs. 33%).

Conclusions

Use of reteplase in AMI at LGH appears to be associated with a shorter median door-to-needle time and less potential for medication errors compared to alteplase. Cost savings may be realized with the appropriate therapeutic choice of reteplase or alteplase over streptokinase in the medical management of AMI.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;11:401.

A Pilot Study to determine the Utility and Feasibility of a Medication Assessment Questionnaire for Opioid and Benzodiazepine Usage in Chronic Non-Malignant Pain Patients

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Objectives

Prescribed opioids are a viable alternative for the treatment of chronic nonmalignant pain (CNMP). However, a subsample of chronic pain patients are at increased risk for opiate and benzodiazepine (BDZ) addiction. At present, no standardized assessment tool exists to assess CNMP patients for opioid or BDZ dependency. The medication assessment questionnaire (MAQ) was developed to determine its feasibility in assessing opioid and benzodiazepine usage in CNMP patients.

Setting

A Canadian 400 bed teaching institution.

Design

CNMP patients admitted to St. Paul's Hospital Pain Center Day Program from September 2001 - March 2002 were included in the study. A MAQ was developed to assess nine domains. The pharmacist conducted the MAQ with each patient and the Pharmanet profile was compared to self-reported usage of opioid and BDZ. The resultant database was analyzed to evaluate the MAQ.

Results

29 patients were included in the study. Four possible sources of errors in the MAQ were identified. Magnitude of missing data was <10%. 21% of questions had no variance. The reliability of the MAQ was assessed using Cronbach's Alpha. In 7/9 domains assessed, Cronbach's alpha was < 0.70.

Conclusions

Modifications to the MAQ are required to improve the credibility, response variability and reliability of the tool in the assessment of opioid and BDZ usage in CNMP patients.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;11:402.

Feasibility of Implementing an Individualized, Evidence Based Stroke Prevention Counseling Program for Patients with Atrial Fibrillation

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 8, 2002.

Objectives

The purpose of this study was to evaluate the feasibility and utility of teaching patients about atrial fibrillation and stroke prevention therapies using individualized, evidence-based information and a handheld computer based tool for risk and benefit estimation.

Setting

A Canadian teaching hospital.

Design

Qualifying patients with atrial fibrillation received information about atrial fibrillation and preventative therapies using qualitative, quantitative and graphical formats. Baseline risk of ischemic stroke and the magnitude of the risks and benefits of each therapeutic alternative were estimated at the bedside using a handheld computer-based tool. Assessments of decisional conflict, atrial fibrillation and stroke knowledge, medication knowledge, feasibility, and therapeutic preferences were performed after the counseling intervention.

Results

Fifty patients were screened and 5 were enrolled. The primary reasons for disqualification were cognitive impairment and length of stay <48 hours. After the counseling intervention, patients tended to prefer warfarin for stroke prophylaxis and there was a low level of decisional conflict. The

intervention took the pharmacist around 30 minutes to perform. The handheld computer risk estimation tool was useful.

Conclusions

The counseling intervention was feasible although a small proportion of patients would qualify according to the criteria used. Those patients who received individualized, evidence-based counseling were knowledgeable about their condition and confident with their decisions regarding drug therapy. A handheld computer-based tool offers an efficient, user-friendly method of estimating an individual's risk for stroke and the effects of preventative therapies in patients with atrial fibrillation.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;11:403.

A Randomized Trial Comparing Two Modalities of Alteplase (tPA) Administration on Hemodialysis Catheter Patency

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 8, 2002.

Objectives

To compare two alteplase (tPA) dwell protocols for clearance of occluded hemodialysis catheters. Although clinical studies support thrombolytics use in catheter clearance, optimal dwell times are not known.

Setting

A 400-bed Canadian teaching hospital.

Design

From October 2001 to May 2002, patients receiving hemodialysis via cuffed or temporary catheter with an episode of catheter dysfunction were randomized to either a short tPA dwell of 1 hour or a long tPA dwell of 48-72h. Restoration of catheter patency (defined as a BPS>250mL/min) at the next dialysis run was the primary outcome. Secondary outcomes included catheter patency two weeks post-tPA, and median catheter function post-tPA.

Results

Of the 60 enrolled patients, 28 were randomized to the 1-hour dwell and 32 to the 48-72 hour dwell. 20 (76.9%) in the short versus 27 (79.4%) in the long dwell met the primary outcome; results were not statistically significant ($p=0.817$). At two weeks, the number of functional catheters declined to 11 (42.3%) in the 1-hour dwell and 18 (52.4%) in the 48-72 hour dwell ($p=0.414$). Median catheter patency

post-tPA was approximately two weeks.

Conclusions

Both tPA dwells appear equally efficacious in immediate catheter clearance with rates consistent with the literature. However, the gradual decline in functional catheters with time suggests that alternatives need to be investigated for long-term catheter management.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;11:404.

Evaluation of a Laxative Withdrawal Protocol in Patients with Anorexia Nervosa and Bulimia Nervosa

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 8, 2002.

Objectives

The purpose of this evaluation is to determine the usefulness and effectiveness of a laxative withdrawal protocol used in a tertiary care regional referral Eating Disorders Program.

Setting

A Canadian 400 bed teaching institution.

Design

Patients were recruited to participate in the laxative withdrawal protocol either as in-patients or out-patients. Patients were followed weekly or every two weeks for six months or until weaned off laxatives.

Results

Ten patients were enrolled with seven patients completing the study. Five out of seven patients (71%) were successful at decreasing their laxative intake by 50%; the average time required was 15.4 ± 7.2 weeks. Three were able to completely withdraw from laxatives; the average time required was 27 ± 2.6 weeks.

Conclusions

The patients who were successful were very motivated to be weaned off laxatives, were more stable with their eating disorder, and used fewer laxatives per day. The patients who were unsuccessful

tended to have a long history of eating disorder and heavy laxative use or were struggling with their eating disorder. In conclusion, the laxative withdrawal protocol appears to be successful in stable out-patients who are highly motivated to be weaned off laxatives.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;11:405.

Drug Utilization Review Of Surgical Prophylaxis In High Risk Cesarean Section

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 8, 2002.

Objectives

Antibiotic prophylaxis can significantly reduce undesirable outcomes in high risk patients undergoing Cesarean Section. Our objective was to determine antibiotic prophylaxis patterns, outcomes and associated cost-savings issues in high risk patients undergoing Cesarean Section.

Setting

A Canadian community hospital.

Design

A retrospective chart review was performed on 275 consecutively selected patients who underwent Cesarean Sections in three hospitals from the Simon Fraser Health Region (SFHR). 171 patients met the criteria.

Results

Rate of antibiotic prophylaxis between three hospitals ranged from 63.3% to 88.2%. Cefazolin or clindamycin was prescribed in 78.5% of cases. Cefotetan was prescribed in 11.5% of cases. Primary endpoint was composite clinical endpoint (CCE), consisting of febrile morbidity, endometritis and wound infection. Antibiotic prophylaxis reduced CCE from 29.3% to 8.5% (RR 0.29, $p < 0.005$). Secondary endpoints were clinical infection (endometritis, wound infection) and endometritis. Antibiotic prophylaxis reduced clinical infection from 22.0% to 4.6% (RR 0.21, $p < 0.005$) and endometritis from

22.0% to 3.8% (RR 0.17, $p < 0.005$). Length of stay (LOS) was reduced from 4.9 days to 3.5 days ($p < 0.05$). Universal antibiotic prophylaxis can result in annual savings of \$3,387 and 95 inpatient-days.

Conclusions

There is significant variation amongst hospitals in the region. Universal antibiotic prophylaxis with cefazolin or clindamycin for all high risk patients undergoing C-section should decrease infection rates, drug expenditures and length of stay.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;11:406.

Assessing The Guidelines For Potassium Replacement In Pediatric Oncology Patients Receiving Amphotericin B

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 8, 2002.

Objectives

To examine the practice of potassium chloride (KCl) replacement in pediatric oncology patients receiving amphotericin B (amp-B); including a review of adherence to the KCl replacement guidelines in our institution as well as a review of the literature and other pediatric institutions' KCl replacement protocols.

Setting

A Canadian teaching institution.

Design

A retrospective chart review was conducted of patients who received amp-B on the oncology ward between August 27, 2000 and May 17, 2001. A literature search was conducted. A survey of pediatric oncology pharmacists at other pediatric institutions was done to assess KCl infusion guidelines in other institutions across North America.

Results

A total of 20 hypokalemic episodes were identified within 22 patient admissions. Of these episodes, 55% used KCl replacement at rates exceeding our institution's current guidelines. Physicians were adherent to providing proper documentation of each episode requiring an interim policy for a rate exceeding our hospital guidelines. A consensus on the maximum rate of KCl that can be safely infused in a non-critical care ward could not be found in the literature. Other pediatric institutions varied with respect to the

maximum rates and concentration of KCl permitted on non-intensive care wards..

Conclusions

Based on the data from this review, the intravenous KCl administration guidelines for our hospital were changed. We now allow a maximum peripheral line concentration of 60 mmol/L (as per current protocol), a maximum central line concentration of 120 mmol/L (increased from 80 mmol/L), and a maximum KCl infusion rate of 0.4 mmol/kg/hr (increased from 0.3 mmol/kg/hr) without the requirement of a heart monitor. TPN is now restricted to maximum concentration of 80 mmol/L and fluid restricted patients are restricted to a maximum concentration of 150 mmol/L. As the methodology of this study provided only an estimation of the KCl requirement in a select population, it is important that the effects from the changes of the new guidelines are frequently monitored. It is also important that physician, nursing, and pharmacy staffs are well educated on the new guidelines and continuously monitor for efficacy and toxicity of IV KCl therapy.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;11:407.

Medication Interruption In Surgical Patients

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 8, 2002.

Objectives

The purpose of the study was to determine if patients are missing regular medications post-operatively and if the missing medications lead the patient to experience drug withdrawal or symptom recurrence that may or may not exacerbate post-operative complications.

Setting

A Canadian teaching hospital.

Design

A 6-month retrospective review comparing patient's medications while in hospital to their medications prior to admission. PharmaNet was used to determine the patient's regular medications prior to admission. If discrepancies between the two lists were found, and the medications could be classified as chronic therapies, the patient's clinical record was evaluated to determine if any subjective or objective evidence of drug withdrawal had occurred.

Results

Forty-three percent of the 47 patients included in the study had medications they were taking prior to admission missing. Three patients (6%) were found to have suffered clinically significant consequences as a result of missing prior medications. The medication class that was most often missed was antidepressants.

Conclusions

Our study population was not large enough to determine the statistical significance of the results. If these results were to occur in a larger sample population we would be able to conclude that undertaking medication histories for all our patients would be a worthwhile endeavour.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;11:408.

Perceptions of Professional Services of a Pharmaceutical Sciences Clinical Service Unit: A Comparison of Stakeholder Groups

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 8, 2002.

Objectives

To determine perceptions of patients, nurses, physicians, and pharmacists regarding the awareness, quality, and priority of professional services offered by the Pharmaceutical Sciences Clinical Services Unit (CSU) at Vancouver General Hospital in the areas of patient care, education and research.

Setting

A major Canadian tertiary adult acute care teaching hospital.

Design

A survey was designed to elicit opinions regarding the awareness, quality, and priority of the drug distribution, clinical, education and research services provided by the CSU. Surveys were distributed over a 90-day period directly to patients and to the mailboxes of nurses, physicians and pharmacists who were affiliated with the hospital. Respondent demographics and responses were analyzed using descriptive statistical analysis.

Results

A total of 2,568 surveys were distributed to all stakeholder groups. Of the 460 surveys analyzed, there were 38 (32%) patient, 276 (16%) nurse, 102 (16%) physician, and 44 (50%) pharmacist respondents. Patient respondents tended to have been in hospital for about two weeks at the time of survey

completion and were located in several practice areas. The duration of employment for nurse, physician and pharmacist respondents was widespread ranging from 1 to 24 years. For nurses and physicians, there was a relatively balanced representation from the medical and surgical practice areas. Most pharmacist respondents practiced in non-surgical areas. Patients were the least aware of the professional services provided by the CSU. The quality of the majority of services was rated as excellent or good across all groups. Respondents ranked the review of prescriptions for appropriateness, the dispensing of oral, intravenous and total parenteral nutrition preparations, the resolution of patient-specific drug distribution issues, group medication sessions, continuing education programs, and the Clinical Drug Research program as the most important professional services.

Conclusions

The study provided information regarding patient, nurse, physician, and pharmacist perceptions regarding awareness, quality, and priority of patient care, education and research services currently offered by the Pharmaceutical Sciences CSU at Vancouver General Hospital and identified areas that require improvement.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;11:409.

Characterizing Patient Discharge Counseling Activities Performed By Hospital Pharmacists

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 8, 2002.

Objectives

To determine how hospital pharmacists identify patients who require discharge counseling and to identify barriers to providing this service.

Setting

A major Canadian tertiary adult acute care teaching hospital.

Design

A survey was distributed to clinical pharmacists at an acute care hospital. They were asked to rank how they identify patients requiring discharge counseling and specific barriers to performing this service. Additional data was collected on discharge activities, such as frequency of documenting patient interviews and liaising with community pharmacists. Opinions regarding the importance of patient discharge counseling were also solicited. Perceptions regarding professional duties and responsibilities of hospital pharmacists were assessed.

Results

The majority ranked prescription of "target drugs" as either the first (50.0%) or second (28.6%) way to identify patients requiring discharge counseling. Almost half surveyed use medication teaching sheets as the primary patient counseling tool. The greatest barriers to providing patient discharge counseling identified were time and workload, followed by patient language. When asked to consider the last 10 patients they had counseled at discharge, two-thirds of pharmacists were able to document 9-10 of the

interviews in the chart; however, most were unable to liaise with the community pharmacist. The majority of pharmacists (71%) very strongly agreed that the pharmacist is the health care professional most qualified to provide medication counseling to hospitalized patients.

Conclusions

This study has gathered data on current opinions and perceptions surrounding patient discharge counseling activities of hospital pharmacists.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;11:410.

Venous Thromboembolism Prevention in Medical Patients with Congestive Heart Failure or Chronic Obstructive Pulmonary Disease

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 8, 2002.

Objectives

To measure the impact of educational interventions on the utilization of thromboprophylaxis as per current guidelines amongst, patients admitted with an exacerbation of congestive heart disease (CHF) or chronic obstructive pulmonary disease (COPD).

Setting

A Canadian community hospital.

Design

Educational interventions in the form of presentations and memos were undertaken in conjunction with 2 physicians to disseminate the findings of venous thromboembolism (VTE) prophylaxis utilization amongst CHF and COPD patients admitted to Lions Gate Hospital and to educate physicians, pharmacists and nurses regarding current practice guidelines for VTE prophylaxis in medical patients. A retrospective analysis of patients admitted with CHF or COPD during a five-month period was conducted following the educational intervention. Furthermore, all physicians were surveyed regarding perceived barriers to VTE prophylaxis amongst CHF and COPD patients.

Results

Following the educational intervention, 46% (n=28) of patients with CHF and 30% (n=33) of patients with COPD received VTE prophylaxis. The survey results revealed that physicians mainly attributed the low rates of prophylaxis to oversight and unawareness of current guidelines.

Conclusions

There are poor rates of VTE prophylaxis amongst patients with CHF and COPD exacerbations at our institution and educational interventions alone were insufficient to ensure the routine use of prophylaxis in clinical practice.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;11:411.

Evaluation of Cardiac Risk Factors in Renal Transplant Recipients

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 8, 2002.

Objectives

Cardiovascular disease (CVD) is the cause of death in almost half of renal transplant recipients with functioning grafts. Cardiac risk factors in general population, such as dyslipidemia are also predictive in transplant patients. The primary objectives of this study were to characterize and stratify cardiac risk factors in renal transplant patients at our outpatient clinic and to develop and implement a dyslipidemia-management protocol in this population.

Setting

A major Canadian tertiary adult acute care teaching hospital.

Design

Medical charts for a total of 98 patients transplanted between Jan 1998 to Oct 2001 were reviewed and cardiac risk factors using Framingham scoring system were determined. A dyslipidemia management protocol was developed based on NCEP Guidelines and a copy of this protocol was inserted in medical records of 42 patients, stating their calculated 10-year cardiac risk percentage and a dyslipidemia treatment option based on NCEP Guidelines.

Results

A significant number of transplant recipients were at intermediate to high risk for developing CVD. Majority of patients had elevated lipids and only a small fraction were receiving antilipid therapy. Our protocol was not effectively utilized as indicated by the small number of patients receiving antilipid therapy.

Conclusions

Considering high prevalence of CVD in transplant patients, aggressive intervention with lipid lowering therapy seems warranted.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;11:412.

Switching from Abciximab to Eptifibatide for Percutaneous Coronary Interventions: A Local Analysis (SWAP Study)

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 8, 2002.

Objectives

Glycoprotein IIb/IIIa inhibitors (GPI) are recommended as adjunctive therapy with percutaneous coronary interventions (PCI). Only abciximab (AB) was available at our institution until October 2000. Thereafter, eptifibatide (EP) was added to formulary and became the preferred agent due to lower cost. Our objective was to describe the impact of switching from AB to EP on prescribing patterns and clinical outcomes following PCI.

Setting

A major Canadian tertiary adult acute care teaching hospital.

Design

Charts of patients who received a GPI with PCI for various indications were reviewed retrospectively. The AB group spanned the 6 months preceding formulary addition of EP in October 2000. A matching number of consecutive patients following this date were included in the EP group.

Results

A total of 160 patients were included (80 per group). Adjunctive GPI usage increased from 11% to 25% of PCI within three months of adding EP to formulary ($p < 0.001$). Compared to AB, EP was associated with more in-hospital ischemic complications (12.5% vs. 2.5%, $p < 0.025$) and minor bleeding ($p = ns$). Premature GPI discontinuation was more common in the EP group (46.3% vs. 7.5%, $p < 0.001$).

Eptifibatide patients had a longer length of hospital stay post-PCI (mean 44.4h vs. 25.1h, $p<0.0001$).

Conclusions

Adjunctive GPI usage more than doubled following introduction of EP to the formulary. Eptifibatide may be associated with inferior clinical outcomes compared to AB for PCI.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2002;11:413.

Multidisciplinary Approach to EPO Resistance in a HD Unit

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 8, 2002.

Objectives

Erythropoietin (EPO) is given for long-term management of serum hemoglobin (Hgb) in hemodialysis (HD) patients at a typical dose of 50-300U/kg/week. Our objectives were to assess risk factors for HD patients receiving EPO doses greater than 300U/kg/week (EPO-resistant) and to determine the effect of downward EPO dosage adjustments on Hgb.

Setting

A major Canadian tertiary adult acute care teaching hospital.

Design

This was an 8-month prospective, open-label study of 19 EPO-resistant patients drawn from a 160-bed HD unit. Hgb, iron studies, intact parathyroid hormone, folate, B12, aluminum, reticulocyte counts and HD flow adequacy were determined at baseline. The former three parameters were followed every 6, 12, and 26 weeks, respectively. Target Hgb was 120-135g/L. Factors contributing to EPO resistance were assessed and treated every 6 weeks, if possible. Downward EPO dosage adjustments of 12.5-25% to the closest 1000U were considered if underlying causes of EPO resistance could not be identified or reversed, or if Hgb rose beyond the target.

Results

Dysfunctional vascular access and iron deficiency were the predominant treatable factors associated with EPO resistance. By study end, mean EPO dosage decreased significantly from 469U/kg/week to 319U/kg/week and mean Hgb increased significantly from 106g/L to 116g/L. The percent of EPO-

resistant patients with a Hgb in the target range rose from 16% at baseline to 63%. Annual cost savings approximated \$157,000.00.

Conclusions

A structured multidisciplinary approach to the management of EPO-resistant patients was successful in significantly lowering EPO dosage with improvement in serum Hgb at a substantial cost savings.

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Journal of Informed Pharmacotherapy 2001;4 (January-March)

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James McCormack, Peter Jewesson



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**Updated
April 15, 2002**

Editorial

The influences around us - be wary of writers' biases

To maintain professional competence in the ever-changing world of health care, we need to become life-long learners. To become a life-long learner, we are obligated to continuously review, critique and integrate new information. The sources of this new information are numerous. A day never goes by without us being exposed to (and probably influenced by) what we have read in the lay press and medical journals; what we have heard on the television and radio; what has been presented to us at seminars and continuing education events; and what we are told by our colleagues and patients.

Unfortunately, every source of information has its inherent biases. Bias is unavoidable because the information being disseminated represents the evidence as interpreted by one or more individuals. Let's face it, there is virtually no way of presenting or interpreting research data without introducing bias. While we are inundated daily with relatively easy to identify examples of the media and the government blatantly falsifying information, and less obvious examples of the drug industry withholding or distorting the data, in general, the biases that we are describing are more subtle, consequently more pervasive, more difficult to detect and potentially even more dangerous.

When we talk about bias, we are referring to both the intentional and unintentional bias that occurs in the delivery of information that draws the authors and readers to reach inaccurate interpretations and conclusions about the data. Whether these preconceptions are innocent or intentional is unimportant. What is critical is that the recipient of this information needs to be acutely aware that these biases exist and that with a dose of healthy skepticism and a little work, the impact of this bias can, at least to some degree, be lessened.

The following are just a few examples of interpretation and presentation biases:

A recent media analysis of 207 stories (television, newspaper) about pravastatin, alendronate, and aspirin revealed that 40% of these stories did not report the quantitative benefits of therapy. (1) Of those that did, 83% of the narratives reported relative benefits only, 2% reported absolute benefits only, and 15% percent reported both. Over one-half (53% to be exact) did not mention the potential harm to patients and 70% of the stories failed to mention the costs of therapy. Of the stories reported, 170 cited an expert or a scientific study, while 50% cited at least one study or expert with a financial tie to the manufacturer. This conflict of interest was disclosed in only 39% of cases. It has shown that reporting information as *relative* benefits only, increases the likelihood that clinicians and patients will choose to use drug therapy. (2,3,4)

Reporters have stated that "we have to almost overstate, we have to come as close as we can within the boundaries of truth to a dramatic, compelling statement". (5) This has been recently illustrated by television media reports of a study published in the New England Journal of Medicine stating that a 16-fold increase in the risk of hemorrhagic stroke was observed for patients who had taken, cough/cold

preparations and dietary aids containing phenylpropanolamine (PPA). (6) These reports were accompanied by dramatic pictures of drug store employees removing these products from the shelves in the interest of public safety. It was quite the sensation, especially when you consider the data behind the hype. First of all, the investigators responsible for the study reported that there was no statistically significant association between hemorrhagic strokes and the use of cough and cold remedies containing PPA. Secondly, the investigators characterized the risk as "...one woman may have a stroke due to PPA for every 107,000 to 3,268,000 women who use PPA as an appetite suppressant within a 3-day window...". While any increased risk is certainly of concern, it is likely that if the media had presented the risk in this objective context, the story would have received different, and probably significantly less press coverage.

Consider the impact of such a media report on the public. Patients often come to us as health professionals and ask our opinion about health care stories reported by the media. One author (JM) has discussed the PPA issue with several parents who had called asking about whether or not it was safe to use cough and cold preparations containing PPA in their children. While their concerns were defused once they were apprised of the actual facts and numbers, they were also surprised to learn that there are actually no published trials that demonstrate these agents have an effect on symptoms in children. In fact, two trials have shown that cough and cold products containing this agent are no more effective on symptoms than placebo when used in children under the age of 6. (7,8) In addition, cough and cold preparations are a common cause of drug overdose cases in children. (9)

There is also considerable evidence of biased reporting in the medical literature. In 1986, Davidson reported on the results of 107 drug trials in leading medical journals. If the drug trials were company funded, 89% favoured the new drug; whereas if the study was non-company funded only 61% favoured the new drug (10). This may also reflect a publication bias.

Interpretation bias is also prevalent in the medical literature. In 1989, Gotzsche reported that of 196 NSAID trials, 76% reported doubtful or invalid statements in the conclusions or abstracts. (11) After an assessment of 56 published NSAID trials, Rochon et al (12) found that 29% reported superior efficacy of one NSAID over another while the remaining 71% reported comparable efficacy. Among those trials claiming superiority, all reported the sponsor's agent as being more efficacious. Of the 22 trials identifying one drug as being less toxic than the other, the manufacturer-associated drug was reported to have a superior safety profile in 86.4% of cases. Only half of the trials reporting less toxicity included any statistical measure to back this claim.

More recently, Stelfox and colleagues reported that of 70 published articles focusing on safety issues of calcium channel blockers, 96% of authors who were supportive of these drugs had financial ties to manufacturers of these agents, whereas only 37% of authors who were critical of the calcium channel blockers had financial ties. (13)

This interpretation bias is not confined to clinical evaluations. In the area of economic analyses, Friedberg et al showed that of 44 economic analyses of oncology drugs, only 5% were unfavourable when funded by the drug industry whereas 38% were unfavourable if the study was not funded by the drug industry. (14)

Recently, one of the authors (JM) reported (15) on the biases associated with the dissemination of the

United Kingdom Prospective Diabetes Study (UKPDS) results. The results of this clinical trial showed firstly that intensive blood glucose control with the use of sulphonylureas or insulin in type 2 diabetics over 10 years had no effect on macrovascular endpoints, diabetes-related deaths or all-cause mortality. Secondly, the results of this trial demonstrated that the use of metformin in overweight type 2 diabetics was associated with a 10% absolute reduction in all micro- and macrovascular complications combined, and a reduction in the incidence of individual macrovascular events in those patients treated with metformin. Amazingly, however, an editorial of this article stated that the UKPDS showed that "clear and consistent evidence now exists that hyperglycemia in diabetes is a continuous, modifiable risk factor for clinically important outcomes and that reduction in glucose is the key to improving outcomes". (16) A fascinating perspective considering the data provided little if any support for this conclusion.

There have been a couple of articles published in reputable journals over the last few months which make it seem like the conclusions were written before the study was complete, as the interpretation of the study results simply didn't match the researcher's own data. In the Archives of Internal Medicine, Bohadana and colleagues (17) describe a trial aimed at determining whether or not a combination of a nicotine inhaler and a nicotine patch was more effective than a nicotine inhaler alone for smoking cessation. The authors concluded that "...treatment with the nicotine inhaler plus nicotine patch resulted in significantly higher cessation rates than inhaler plus placebo patch". However, their data showed that while there were statistically significant differences between treatment arms at 1 and 3 months, there were no differences between treatments at 6 months and 1 year.

In an article published in the British Medical Journal, (18) researchers looked at the combination of candesartan and lisinopril compared to treatment with either agent alone in patients with diabetes and hypertension. The investigators state in their abstract that "reduction in urinary albumin:creatinine ratio with combination [candesartan plus lisinopril] was greater than with candesartan and lisinopril [as single agents]" and actually present p-values. However in the abstract they presented the p-values for the differences from baseline for the groups, not the p-values for the comparison between the groups. In the body of the article itself, the data presented reveals that the difference in the urinary albumin:creatinine ratio between lisinopril and the combination was not significant ($p>0.20$). In other words, they did not show that the combination was more effective than lisinopril alone. The p value for the difference between candesartan and the combination was 0.04. As numerous statistical tests were done, and no correction for multiple testing was applied, a p-value of 0.04 is of questionable significance.

So what is the take-home message? The examples we have discussed are intended to simply illustrate that biases are well entrenched in published medical information and that as health care professionals, we need to be aware of these and be skeptical health care information consumers. If you are thinking of changing your practice based on something you have read or heard, don't dive in until you know how deep the water is. Don't rely on others to interpret the data for you. Take the time to read the original research report yourself. You'll be surprised how often your interpretation of the clinical importance of the results differs from those of the investigators, the editorialists and even your colleagues.

Always remember that everyone with an interest in health care has a perspective and everyone with a perspective has an inherent bias. That includes the government, the media, the drug industry, the universities, and even the authors of this editorial. Look at the results for yourself and form your own conclusions.

James McCormack, PharmD, Peter J. Jewesson, PhD FCSHP

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Original Research Article

Validation of an unfractionated heparin nomogram using an anti-factor Xa chromogenic assay

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Abstract

Objective: The objective of this study was to develop and evaluate an unfractionated heparin dosing nomogram based up on a chromogenic anti-Xa assay and to employ this nomogram for patients presenting with either venous or coronary thrombosis.

Design: A prospective, two-phase cohort study design.

Setting: Intensive care unit, coronary care unit, emergency department.

Participants: Patients presenting with coronary or venous thrombosis.

Interventions: A heparin dosing nomogram was developed and implemented. Pre-printed nomograms were completed by the prescribing physician. Nurses were responsible for

performing dosage adjustments and drawing bloodwork as specified in the nomogram.

Main Outcome measures: The percentage of patients with a therapeutic anti-factor Xa chromogenic heparin assay level at 24 hours, the time required to exceed the minimum therapeutic threshold (>0.35 U/mL), time to obtain the therapeutic range, time to stabilization within the therapeutic range, and incidence of bleeds.

Results: In the first phase (the pilot phase) ($n=7$) the primary outcome was attained by 28.6% of patients. The majority of patients were supratherapeutic at 6, 12, and 24 hours. These results suggested that the nomogram dosing was too aggressive, and thus the nomogram was modified for the second phase. Nineteen patients were included in the assessment of the modified nomogram. The percentage of patients who were therapeutic vs. supratherapeutic at 24 hours was 36.8% and 57.9%, respectively. Thus, 94.7% of patients exceeded the therapeutic threshold at 24 hours. Fifteen patients (79%) were stabilized within the therapeutic range, with a mean time to stabilization of 25.0 ± 8.6 hours. There were no reports of major bleeds.

Conclusions: The modified nomogram was successful in exceeding the therapeutic threshold both rapidly and safely. Most patients subsequently settled within the therapeutic range. This nomogram is now routinely used at our center.

J Inform Pharmacother 2001;4:100-9.

Introduction

Several heparin dosing nomograms based on patient weight and activated partial thromboplastin time aPTT have been developed and compared with empiric dosing by physicians. (5-10) The advantages of these nomograms include individualization of initial dosing, standardization of dosage adjustments and structured monitoring. Furthermore, patients who were dosed according to a nomogram had a greater chance of attaining a therapeutic aPTT with the first measurement at six hours, achieved a more rapid therapeutic aPTT, and exceeded the therapeutic threshold sooner compared to those receiving standard dosing. On the other hand, patients were more likely to experience a supratherapeutic aPTT within the first 24 hours. (5, 6, 9, 10) However, there was either no difference in the frequency of bleeding between standard and nomogram-based heparin dosing or no documentation of bleeding complications. (5-7, 9, 10)

The anti-Xa chromogenic heparin assay (ACCUCOLOR(TM)) is based on the heparin-

accelerated neutralization of the activated serine protease factor Xa. (4) Our institution has been using the heparin assay since August of 1998. A therapeutic level is considered to be in the range of 0.35 to 0.67 U/mL. Unlike the aPTT, the anti-Xa heparin assay specifically measures the biologic activity of heparin and is thus unaffected by concomitant therapy with warfarin or thrombolytics or by altered levels of coagulation factors.¹ Acute phase reactants, factor VIII and fibrinogen, which are usually increased in patients with thromboembolic disease, may lead to a decreased response of the aPTT. (1) Antithrombin deficiency, which may manifest as heparin resistance, or increased levels of heparin binding proteins may also lead to a decreased response. (1) Alternatively, patients with mild reductions of multiple coagulation factors have an increased response of the aPTT. The presence of lupus anticoagulants and deficiencies in factor XII, prekallikrein, and high-molecular-weight kininogen lead to prolongation of the baseline aPTT. The aPTT may also be unreliable in patients with overwhelming infections, myocardial infarctions, or severe liver disease. (2)

Heparin assays may be reliable in patients presenting with a prolonged baseline aPTT. (1) However, heparin assay results are affected by age, obesity, increased levels of heparin binding proteins, hepatic or renal disease, and general heparin resistance. It is also unknown whether heparin assays are superior to aPTT testing in patients with liver disease or consumptive coagulopathies. In addition, heparin assays have limited availability and are more expensive to perform than the aPTT test. (1,3)

Levine et al. have compared a heparin-dosing nomogram, based on chromogenic anti-factor Xa heparin assay results, but not patient weight, to the aPTT for monitoring response to therapy in patients with heparin resistance.⁽¹³⁾ They concluded that many patients who were heparin resistant according to the aPTT were, in fact, therapeutic according to the heparin assay. There was a greater incidence of bleeds in the group monitored by the aPTT although this difference was not statistically significant.

Prior to this study at our institution, adjustments in heparin infusion rates in response to non-therapeutic heparin assays were made at the discretion of the physician. Nursing staff informed the physician of all heparin assay levels and awaited a new order before adjusting the infusion rate. It was felt that with the implementation of a heparin dosing nomogram based on patient weight and heparin assay results, therapeutic heparin assay levels could be achieved more quickly and more efficiently.

The objective of this study was to develop and evaluate an unfractionated heparin dosing nomogram based upon a chromogenic anti-Xa assay and to employ this nomogram for patients presenting with either venous or coronary thrombosis.

Methodology

Study design

A prospective, two-phase cohort design was used. The first phase involved the enrollment of a small pilot patient population to initially assess the effectiveness of the nomogram in achieving therapeutic heparin assays. The results from this pilot study were then used to determine if any changes to the nomogram were warranted. The second phase involved validating the modified nomogram using a larger patient population. For this phase, it was decided to enroll only those patients presenting with acute coronary syndromes as very few venous thrombosis patients were being initiated on unfractionated heparin.

The pharmacy investigator met with several individuals before the nomogram was distributed to the emergency department (ED), intensive care unit (ICU), and coronary care unit (CCU). In these areas, the head nurse, nursing team leaders, and nursing staff were informed of the study. In addition, the study was explained to ICU and cardiology medical staff.

Patients

The study population consisted of patients admitted to The Ottawa Hospital (General Campus) with a diagnosis of either venous or coronary thrombosis and who were initiated on intravenous unfractionated heparin. Therapy was begun in either the ICU, CCU, or ED.

Inclusion criteria were as follows: patients greater than 18 years of age diagnosed with either coronary or venous thrombosis, admitted to either the ICU, CCU, or ED and expected to receive at least 24 hours of unfractionated heparin therapy. Exclusion criteria consisted of obesity (i.e. greater than or equal to 130% of ideal body weight), increased risk of bleeding, history of heparin-induced thrombocytopenia (HIT), documented allergy to heparin, or thrombocytopenia (platelet count less than 100×10^9 g/L prior to therapy).

Each patient was assessed for risk of a major bleed (see data collection). It was left up to the physician to determine a patient's risk of bleeding and whether he/she should be initiated on the heparin nomogram.

Patient consent was not deemed necessary as no randomization occurred. Moreover, this

study was conducted as a continuous quality assurance program for the ICU, rather than as a clinical research protocol.

Heparin Nomogram

The initial nomogram designed by the department of hematology was based on patient weight, anti-Xa heparin assay results, and indication for heparin, either venous or coronary thrombosis. Deep venous thrombosis (DVT) clots are generally known to be larger than coronary artery clots. Also, given the burden of thrombus and involved tissue in DVT patients, there may be greater activation of acute phase reactants, which are known to bind to heparin. Therefore, patients presenting with venous thrombosis may initially have increased heparin requirements and thus higher loading doses were prescribed.

Pre-printed order forms were distributed to the ED, CCU, and ICU to be completed by the prescribing physician. The physician determined the initial heparin bolus and infusion rate based on patient weight and indication for heparin therapy. Baseline laboratory tests (international normalized ratio (INR), complete blood count (CBC) and aPTT) were ordered as specified in the nomogram. Six hours after the initial heparin bolus, the anti-Xa heparin assay was determined. Based on the results of the first and subsequent heparin assays, nurses took appropriate action as directed by the nomogram without involving the physician. The CBC was repeated daily while the patient was receiving heparin therapy. Heparin assays were reordered 6 hours following each dosage adjustment and daily if no dosage adjustments were made. The therapeutic range of 0.35 to 0.67 U/ml for the heparin assay was the same as used by Levine et al. (13)

Data Collection

Demographic data including age, actual body weight, sex, reason for initiation of heparin therapy, concomitant disease states, bleeding risk, and indication for heparin therapy as well as baseline laboratory values (INR, platelets, hemoglobin, and heparin assay), date, time and location of initiation of heparin therapy, initial bolus and infusion rate, and results of all heparin assays were recorded. Next, the following were determined: time to reach the therapeutic range (0.35-0.67 U/mL) following initiation of therapy, time to stabilization (as defined by the time to reach the first of two consecutive therapeutic heparin assays) following initiation of therapy, total number of adjustments required to achieve stabilization, duration of heparin therapy, adverse events, and compliance.

Risk factors for a major bleed were defined by at least one of the following criteria: major surgery in the preceding 7 days, coagulation defects (baseline INR >1.2), gastrointestinal bleed or cerebral hemorrhage in the previous 3 months, uncontrolled hypertension (SBP >180 mmHg and/or DBP >120mmHg), thrombolytic therapy in the preceding 7 days, or concurrent antiplatelet therapy (including NSAID and ASA). (8)

Adverse events (type and action taken) were recorded as either a major or minor bleeding episode or other (i.e. thrombocytopenia). A major bleeding episode was defined as meeting one or more of the following criteria: a decrease in hemoglobin of more than 20 g/L, transfusion of two or more units of blood, or bleeding in the retroperitoneum, cranium, or prosthetic joint. A minor bleeding episode was defined as a bleed not meeting any of the criteria of a major bleed.⁵

Outcomes

The primary outcome measure was the percentage of patients whose heparin assay results fell within the therapeutic range (0.35-0.67 U/mL) at 24 hours. Secondary outcome measures included the percentage of patients whose assay results fell within the therapeutic range at 6, 12, and 48 hours, the time required to exceed the minimum therapeutic threshold (>0.35 U/mL), the percentage of patients stabilized within the therapeutic range at 12, 24, and 48 hours, the time required to stabilization within the therapeutic range, the percentage of supratherapeutic assays (> 0.67 U/mL) at 6, 12, 24, and 48 hours, the mean number of adjustments per patient to achieve stabilization within the therapeutic range, and the success rate of achieving a therapeutic assay following a dosage adjustment.

Analysis

Descriptive statistics were used to evaluate the data. Non-compliance with the nomogram was assessed by the number and severity of deviations from the nomogram. Criteria for excluding patients included any of the following: incorrect initial bolus and/or infusion rate, omission of first or subsequent heparin assays, incorrect dosage adjustment, first heparin assay drawn greater than 2 1/2 hours late or early, or any subsequent assay drawn greater than 4 hours late or 2 hours early.

Results

First Phase

During this phase, 39 patients were initiated on the nomogram. The majority were excluded from the analysis for the following reasons: 19 patients were excluded due to the temporary unavailability of the heparin assay from the hematology laboratory, 8 patients were excluded based on gross non-compliance with the nomogram, 4 patients were excluded based on obesity, and 1 patient was excluded due to the unavailability of the chart. The remaining 7 patients, all cardiology patients, were included in the initial analysis.

The mean duration of heparin therapy for these 7 patients was 75.2 +/- 91.4 hours (range 22.3-278.6 hours). Only 2 patients (28.6%) were within the therapeutic range at 24 hours and thus attained the primary outcome. At 6, 12, and 48 hours, the percentages of patients within the therapeutic range were 14.3%, 14.3%, and 66.7%, respectively. The remaining patients had supratherapeutic assays at these times. Overall, 40 heparin assays were performed. Of these assays, 27.5% were therapeutic and 65% were supra-therapeutic.

Time to exceed the therapeutic threshold was 6.4 +/- 1.4 hours (range 3.8- 8.3 hours). Three patients remained supratherapeutic for the duration of heparin therapy and thus never reached the therapeutic range. Of the 4 remaining patients who did achieve the therapeutic range, they did so with a mean time of 21.2 +/- 17.4 hours (range 3.8-44.7 hours). Only 1 patient was stabilized within the therapeutic range, with a time to stabilization of 41.7 hours. Length of heparin therapy in this patient was 278.6 hours.

One patient experienced a large hematoma on the left flank on the third day of heparin therapy with a drop in hemoglobin of 53 g/L, necessitating discontinuation of heparin therapy. This patient had also received treatment with alteplase on arrival to the hospital. The first two heparin assays were greater than 0.8 U/mL.

Based on these results, it was decided that the nomogram should be modified and made less aggressive. The revised nomogram retained the same heparin loading dose formula, however the initial maintenance dose infusion rates were decreased. (Figure 1) Furthermore, the second phase of the study was limited to cardiology patients with acute coronary syndromes since very few venous thrombosis patients were being treated with unfractionated heparin.

Second Phase

The nomogram used in the second phase of the study is shown in [Figure 1](#).

Forty-four patients were initiated on the nomogram over approximately a one month period during the second phase of the study. In total, 25 patients had to be excluded from the data analysis for the following reasons: obesity (8), duration of heparin therapy less than 24 hours (5), indication for heparin other than coronary thrombosis (2), already receiving heparin (2), and marked non-compliance with the nomogram (16). Some patients may have been excluded based on more than one criteria. Data for remaining 19 patients were used to assess the efficacy of the nomogram (Table 1). Characteristics of these patients are presented in Table 1. A total of 95 assays was reported by the hematology laboratory. Of these, 47 (49.5%), 41 (43.2%), and 7 (7.4%) assays were therapeutic, supratherapeutic, and subtherapeutic, respectively.

Table 1. Patient characteristics during the second phase

Age (y)*	
Male	64.6 +/- 11.3 (44-80)
Female	75.4 +/- 8.2 (67-89)
Sex	
Male	10
Female	9
Weight (kg)	
Male	76.3 (65-94)
Female	57.7 (41-73)
Reason for initiation of heparin:	
Unstable angina	8
Acute myocardial infarction	11
Risk factors for a major bleed:	
0	2
1	10
2	6
3	1
Location of initiation of heparin:	
ED	14
ICU/CCU	5

Concomitant disease states:

Coronary artery disease	7
Congestive heart failure	1
Prior stroke/Transient ischemic attack	3
Hypertension	6
Dyslipidemia	3
Peripheral vascular disease	2
Diabetes	4
Renal insufficiency	3
Anemia	1
Malignancy	3
Other	20

Baseline laboratory values*

aPTT (s)	32 +/- 6 (25-48)
INR	1.11 +/- 0.20 (0.91-1.60)
Platelets (/L)	244 +/- 72 (117-395)
Hemoglobin (g/L)	131 +/- 15 (129-135)

*Data presented as mean +/- standard deviation, range in parentheses.

The primary outcome, the percentage of patients whose assay results fell within the therapeutic range (0.35-0.67 U/mL) at 24 hours, was 36.8% (Table 2). The percentage of patients whose assay results were therapeutic at 6, 12, and 48 hours was 15.8%, 21.1%, and 83.3%, respectively. The percentage of patients whose assays were supratherapeutic at 6, 12, 24, and 48 hours was 84.2%, 78.9%, 57.9%, and 8.3%, respectively (Table 2). Table 3 further outlines the degree to which the assays were supratherapeutic. The magnitude of elevation of the supratherapeutic assays tended to diminish with time. The mean duration of heparin therapy was 60.1 +/- 19.2 hours (range 25.6-97.3).

Table 2. Number of patients therapeutic, supratherapeutic, and subtherapeutic at 6, 12, 24, and 48 hours during second phase

	6 hours (n=19)	12 hours (n=19)	24 hours (n=19)	48 hours (n=12)
Therapeutic (%)	3 (15.8)	4 (21.1)	7 (36.8)	10 (83.3)
Supratherapeutic (%)	16 (84.2)	15 (78.9)	11 (57.9)	1 (8.3)
Subtherapeutic (%)	0	0	1 (5.3)	1 (8.3)

Time to exceed the therapeutic threshold and to obtain the therapeutic range were 6.2 +/- 0.8 hours (range 5.3-8.0) and 23.0 +/- 10.0 hours (range 5.4-35.5), respectively. The mean number of dose adjustments required to achieve the first therapeutic assay was 2.1 +/- 1.3 (range 0-4). In total, 15 patients had assay results stabilized within the therapeutic range. The percentage of patients whose assay results stabilized within the therapeutic range by 12, 24, and 48 hours was 5.3%, 26.3%, and 75%, respectively (Table 3). The mean number of dosage adjustments required to achieve stabilization was 2.2 +/- 0.8 (range 0-4). The mean time to stabilization within the therapeutic range was 25.0 +/- 8.6 hours (range 5.4-35.5). However, of these 15 patients, only 11 remained within the therapeutic range until heparin therapy was discontinued. Of the remaining 4 patients, 3 had subtherapeutic results while 1 had supratherapeutic results. Of the 4 patients who were never stabilized in the therapeutic range, 2 had their heparin therapy discontinued after the first therapeutic assay, 1 received heparin for 25.6 hours and had only 1 assay drawn, and the other patient was subtherapeutic following both supratherapeutic and therapeutic results.

Table 3. Magnitude of elevation of the supratherapeutic assays at 6,12, 24, and 48 hours during second phase

	6 hours (n=16)	12 hours (n=15)	24 hours (n=11)	48 hours (n=1)
0.68 - 0.74 U/mL	4	6	9	1
0.75 - 0.79 U/mL	6	5	2	0
>0.79 U/mL	9	4	0	0

The success rate of achieving a therapeutic assay following one dosage adjustment was 43.2%. In the 16 patients who were not therapeutic at 6 hrs (all were supratherapeutic), the first dosage adjustment was successful in 3, leading to a subsequent therapeutic heparin assay. The remaining 81.2% of assays remained supratherapeutic after dosage adjustment.

There were no major bleeds among the patients included in the data analysis. However,

8 patients experienced minor bleeds and/or bruising, including the 5 patients who had received treatment with alteplase (tPA). These 5 patients had at least one other risk factor for a bleed (e.g. daily ASA). One chronic ASA user also had an initial INR of 1.53. The remaining 3 patients who had not received tPA had also had at least one risk factor for a bleed (daily ASA +/- initial INR > 1.2). Types of bleeds included: rectal bleed (1 patient), epistaxis (2 patients), and bleeding at new/old intravenous site (3 patients). There were no reports of heparin-induced thrombocytopenia.

Complete compliance with the nomogram was achieved in 5 patients. In the remaining 14 patients, a total of 27 minor deviations occurred.

Discussion

The nomogram used in the first phase of the study was successful in rapidly exceeding the therapeutic threshold. However, there was a high percentage of supratherapeutic assays, and not all patients reached the therapeutic range. Nonetheless, the results from this small patient sample were valuable as they indicated that the nomogram to be used in the second phase should be made less aggressive.

The modified nomogram used in the second phase of the study proved to be effective in rapidly and safely exceeding the therapeutic threshold as 36.8% of patients attained the primary outcome and the mean time to obtain the therapeutic range was 23.0 hours. Furthermore, the majority of patients were stabilized within the therapeutic range with a mean time of 25.0 hours. One patient was stabilized by as quickly as 5.4 hrs since the first heparin assay was drawn in the late evening, approximately 7 hours before the daily heparin assay, drawn in the early morning.

In general, patients in the second phase tended to be supra-therapeutic with the first 1 to 3 assays before achieving the therapeutic range. The percentage of patients supra-therapeutic at 24 hours was 57.9%. Despite these results, there was no evidence of any major bleeds. In fact, studies involving patients with venous thrombosis have not clearly demonstrated that excessive anticoagulation with heparin during the first few days of therapy is associated with an increased risk of bleeding.¹⁵ However, there is sufficient proof that serious bleeding may result despite therapeutic anticoagulation with heparin.¹⁶ In the first phase of the study, 1 patient experienced a major bleed. However, this patient had also received treatment with alteplase which may have been contributory. Despite the many supra-therapeutic assays and the concomitant use of alteplase in 5 patients, there were no major bleeds associated with the modified

nomogram used in the second phase.

In one study which examined the use of an aPTT-based heparin nomogram in coronary patients, 72.5% of patients had assays which were within the therapeutic range at 24 hours as compared to 36.8% of patients in the present study. (9) The discrepancy in results may be explained by the fact that the previous study made dosage adjustments based on units/kg/hour. As compared to the present study, this method of dosage adjustment may be more precise in achieving the therapeutic range at 24 hours. With the aPTT-based nomogram, only 72.5% exceeded the therapeutic threshold within 12 hours whereas all patients in the present study exceeded the therapeutic threshold with a mean time of 6.15 hours. Furthermore, 33% of patients in the previous study had an initial supratherapeutic aPTT as compared to 84.2% of patients in the present study. However, the present study aimed to rapidly exceed the therapeutic threshold and thus used higher loading doses which may explain this higher percentage of initially supratherapeutic assays.

In a second study which evaluated the use of an aPTT-based nomogram in a coronary care unit, the times to exceed the therapeutic threshold and to achieve a therapeutic aPTT were 6.7 hours and 20.8 hours, respectively. (10) These values are comparable to the times of 6.15 and 22.96 hours found in the present study. In contrast, at 24 hours, more patients were therapeutic and fewer were supra-therapeutic than in the present study, 51% vs. 36.8% and 38.3% vs. 57.9%, respectively. These differences may be explained by the less aggressive dosing used in the previous study, a fixed bolus of 5000 units followed by an initial infusion rate of 15 units/kg/hour.

Recently, a pharmacoeconomic study was carried out to determine the costs of monitoring unfractionated heparin therapy by the anti factor Xa assay compared to the aPTT test. (3) Although the 96-hour assay cost using the heparin assay was 16% higher than with the aPTT test, the group monitored with the heparin assay had significantly fewer tests and dosage adjustments. This reduction in the number of tests and dosage adjustments compensated for most of the increased costs associated with the assay. The investigators concluded that, given the anti-Xa heparin assay advantages over the aPTT test in certain groups of patients and the modestly increased costs, the assay should be used to monitor unfractionated heparin therapy in most large hospitals.

The present study did not consider the possible interaction between heparin and intravenous nitroglycerin, leading to decreased heparin efficacy as demonstrated by the aPTT results. This interaction is of questionable significance and if it does occur, it is usually at higher doses of nitroglycerin. (17) Furthermore, the interaction has been

reported only with the aPTT test, not with the heparin assay. Even if such an interaction occurred in our study population, the present study focused on the timeframe required to achieve the therapeutic range, rather than the exact results of the heparin assays.

Limitations of this study included the small sample size. Unfortunately, the hematology laboratory was unable to perform heparin assays for approximately two thirds of the initial phase due to a lack of reagent from the supplier. Furthermore, approximately 36% of patients initiated on the heparin nomogram during the second phase of the study had to be excluded from the data analysis due to non-compliance with the nomogram. Perfect compliance was achieved in only 5 patients. There was reluctance on the part of physicians to prescribe the recommended loading doses and initial infusion rates as dictated by the nomogram as these differed significantly from the customary 5000 unit loading dose and 1000 unit/hour maintenance infusion. In total, 7 patients were excluded based on either an incorrect loading dose, initial infusion rate, or both. The tendency also existed to make dosage adjustments based on non-therapeutic aPTT results, despite therapeutic heparin assays. Other instances of non-compliance included assays either drawn at inappropriate times or omitted altogether, inappropriate dosage adjustments or dosage adjustments not done when indicated, and missing heparin assay results. The lack of compliance may have been due to nursing time constraints and laboratory delays in providing heparin assay results. In addition, the inability of an investigator able to monitor active patients on a 24 hour basis would have played a key role in increasing compliance with the nomogram. However, it may be argued that since the evaluation of the nomogram was conducted as an effectiveness trial rather than as an efficacy trial, the low compliance rate more accurately reflects clinical practice.

Secondly, the lack of a control group does not permit any direct comparisons to be made between nomogram and empiric dosing in terms of efficacy and safety. Thirdly, this study was designed to use heparin assay results, and not patient outcomes, as endpoints. Lastly, this study examined the use of the nomogram in non-obese cardiology patients. Thus, extrapolation of these results to obese patients as well as to patients receiving heparin for indications other than coronary thrombosis may not be feasible. For example, as previously mentioned, patients initially presenting with deep venous thrombosis often have increased heparin requirements. Patients at increased risk of bleeding, such as stroke patients, may suffer more serious consequences if they should experience a bleed.

Positive feedback regarding the nomogram was received from both nursing and cardiology staff. Nurses appreciated the autonomy of making dosage adjustments without the need to contact cardiology staff. In turn, cardiology staff was satisfied that patients were attaining the therapeutic range and that there were no major bleeds attributed to

heparin therapy. In addition, other services, including vascular surgery and family medicine, expressed interest in the nomogram. The nomogram which was implemented throughout the hospital was slightly modified. It was decided to treat a heparin assay of greater than 0.8 U/mL more aggressively by holding the infusion for 1 hour and then decreasing the rate by 250 U/hr, rather than 200 U/hr.

Conclusions

The final nomogram was successful in rapidly and safely exceeding the therapeutic threshold. Although evaluated only in cardiology patients, the use of this nomogram was implemented throughout the hospital for use in non-obese patients at low risk of bleeding presenting with either coronary or venous thrombosis.

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Original Research Article

Validation of an unfractionated heparin nomogram using an anti-factor Xa chromogenic assay

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Abstract

Objective: The objective of this study was to develop and evaluate an unfractionated heparin dosing nomogram based up on a chromogenic anti-Xa assay and to employ this nomogram for patients presenting with either venous or coronary thrombosis.

Design: A prospective, two-phase cohort study design.

Setting: Intensive care unit, coronary care unit, emergency department.

Participants: Patients presenting with coronary or venous thrombosis.

Interventions: A heparin dosing nomogram was developed and implemented. Pre-printed nomograms were completed by the prescribing physician. Nurses were responsible for performing dosage adjustments and drawing bloodwork as specified in the nomogram.

Main Outcome measures: The percentage of patients with a therapeutic anti-factor Xa chromogenic heparin assay level at 24 hours, the time required to exceed the minimum therapeutic threshold (>0.35 U/mL), time to obtain the therapeutic range, time to stabilization within the therapeutic range, and incidence of bleeds.

Results: In the first phase (the pilot phase) (n=7) the primary outcome was attained by 28.6% of patients. The majority of patients were supratherapeutic at 6, 12, and 24 hours. These results suggested that the nomogram dosing was too aggressive, and thus the nomogram was modified for the second phase. Nineteen patients were included in the assessment of the modified nomogram. The percentage of patients

who were therapeutic vs. supratherapeutic at 24 hours was 36.8% and 57.9%, respectively. Thus, 94.7% of patients exceeded the therapeutic threshold at 24 hours. Fifteen patients (79%) were stabilized within the therapeutic range, with a mean time to stabilization of 25.0 ± 8.6 hours. There were no reports of major bleeds.

Conclusions: The modified nomogram was successful in exceeding the therapeutic threshold both rapidly and safely. Most patients subsequently settled within the therapeutic range. This nomogram is now routinely used at our center.

J Inform Pharmacother 2001;4:100-9.

Several heparin dosing nomograms based on patient weight and activated partial thromboplastin time aPTT have been developed and compared with empiric dosing by physicians. (5-10) The advantages of these nomograms include individualization of initial dosing, standardization of dosage adjustments and structured monitoring. Furthermore, patients who were dosed according to a nomogram had a greater chance of attaining a therapeutic aPTT with the first measurement at six hours, achieved a more rapid therapeutic aPTT, and exceeded the therapeutic threshold sooner compared to those receiving standard dosing. On the other hand, patients were more likely to experience a supratherapeutic aPTT within the first 24 hours. (5, 6, 9, 10) However, there was either no difference in the frequency of bleeding

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between standard and nomogram-based heparin dosing or no documentation of bleeding complications. (5-7, 9, 10)

The anti-Xa chromogenic heparin assay (ACCUCOLOR™) is based on the heparin-accelerated neutralization of the activated serine protease factor Xa. (4) Our institution has been using the heparin assay since August of 1998. A therapeutic level is considered to be in the range of 0.35 to 0.67 U/mL. Unlike the aPTT, the anti-Xa heparin assay specifically measures the biologic activity of heparin and is thus unaffected by concomitant therapy with warfarin or thrombolytics or by altered levels of coagulation factors.¹ Acute phase reactants, factor VIII and fibrinogen, which are usually increased in patients with thromboembolic disease, may lead to a decreased response of the aPTT. (1) Antithrombin deficiency, which may manifest as heparin resistance, or increased levels of heparin binding proteins may also lead to a decreased response. (1) Alternatively, patients with mild reductions of multiple coagulation factors have an increased response of the aPTT. The presence of lupus anticoagulants and deficiencies in factor XII, prekallikrein, and high-molecular-weight kininogen lead to prolongation of the baseline aPTT. The aPTT may also be unreliable in patients with overwhelming infections, myocardial infarctions, or severe liver disease. (2)

Heparin assays may be reliable in patients presenting with a prolonged baseline aPTT. (1) However, heparin assay results are affected by age, obesity, increased levels of heparin binding proteins, hepatic or renal disease, and general heparin resistance. It is also unknown whether heparin assays are superior to aPTT testing in patients with liver disease or consumptive coagulopathies. In addition, heparin assays have limited availability and are more expensive to perform than the aPTT test. (1,3)

Levine et al. have compared a heparin-dosing nomogram, based on chromogenic anti-factor Xa heparin assay results, but not patient weight, to the aPTT for monitoring response to therapy in patients with heparin resistance.⁽¹³⁾ They concluded that many patients who were heparin resistant according to the aPTT were, in fact, therapeutic according to the heparin assay. There was a greater incidence of

bleeds in the group monitored by the aPTT although this difference was not statistically significant.

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The study population consisted of patients admitted to The Ottawa Hospital (General Campus) with a diagnosis of either venous or coronary thrombosis and who were initiated on intravenous unfractionated heparin. Therapy was begun in either the ICU, CCU, or ED.

Inclusion criteria were as follows: patients greater than 18 years of age diagnosed with either coronary or venous thrombosis, admitted to either the ICU, CCU, or ED and expected to receive at least 24 hours of unfractionated heparin therapy. Exclusion criteria consisted of obesity (i.e. greater than or equal to 130% of ideal body weight), increased risk of bleeding, history of heparin-induced thrombocytopenia (HIT), documented allergy to heparin, or thrombocytopenia (platelet count less than 100×10^9 g/L prior to therapy).

Each patient was assessed for risk of a major bleed (see data collection). It was left up to the physician to determine a patient's risk of bleeding and whether he/she should be initiated on the heparin nomogram.

Patient consent was not deemed necessary as no randomization occurred. Moreover, this study was conducted as a continuous quality assurance program for the ICU, rather than as a clinical research protocol.

Heparin Nomogram

The initial nomogram designed by the department of hematology was based on patient weight, anti-Xa heparin assay results, and indication for heparin, either venous or coronary thrombosis. Deep venous thrombosis (DVT) clots are generally known to be larger than coronary artery clots. Also, given the burden of thrombus and involved tissue in DVT patients, there may be greater activation of acute phase reactants, which are known to bind to heparin. Therefore, patients presenting with venous thrombosis may initially have increased heparin requirements and thus higher loading doses were prescribed.

Pre-printed order forms were distributed to the ED, CCU, and ICU to be completed by the prescribing physician (Appendix 1). The physician determined the

initial heparin bolus and infusion rate based on patient weight and indication for heparin therapy. Baseline laboratory tests (international normalized ratio (INR), complete blood count (CBC) and aPTT) were ordered as specified in the nomogram. Six hours after the initial heparin bolus, the anti-Xa heparin assay was determined. Based on the results of the first and subsequent heparin assays, nurses took appropriate action as directed by the nomogram without involving the physician. The CBC was repeated daily while the patient was receiving heparin therapy. Heparin assays were reordered 6 hours following each dosage adjustment and daily if no dosage adjustments were made. The therapeutic range of 0.35 to 0.67 U/ml for the heparin assay was the same as used by Levine et al. (13)

Data Collection

Demographic data including age, actual body weight, sex, reason for initiation of heparin therapy, concomitant disease states, bleeding risk, and indication for heparin therapy as well as baseline laboratory values (INR, platelets, hemoglobin, and heparin assay), date, time and location of initiation of heparin therapy, initial bolus and infusion rate, and results of all heparin assays were recorded. Next, the following were determined: time to reach the therapeutic range (0.35-0.67 U/mL) following initiation of therapy, time to stabilization (as defined by the time to reach the first of two consecutive therapeutic heparin assays) following initiation of therapy, total number of adjustments required to achieve stabilization, duration of heparin therapy, adverse events, and compliance.

Risk factors for a major bleed were defined by at least one of the following criteria: major surgery in the preceding 7 days, coagulation defects (baseline INR >1.2), gastrointestinal bleed or cerebral hemorrhage in the previous 3 months, uncontrolled hypertension (SBP >180 mmHg and/or DBP >120 mmHg), thrombolytic therapy in the preceding 7 days, or concurrent antiplatelet therapy (including NSAID and ASA). (8)

Adverse events (type and action taken) were recorded as either a major or minor bleeding episode or other (i.e. thrombocytopenia). A major bleeding episode was defined as meeting one or more of the

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following criteria: a decrease in hemoglobin of more than 20 g/L, transfusion of two or more units of blood, or bleeding in the retroperitoneum, cranium, or prosthetic joint. A minor bleeding episode was defined as a bleed not meeting any of the criteria of a major bleed.⁵

Outcomes

The primary outcome measure was the percentage of patients whose heparin assay results fell within the therapeutic range (0.35-0.67 U/mL) at 24 hours. Secondary outcome measures included the percentage of patients whose assay results fell within the therapeutic range at 6, 12, and 48 hours, the time required to exceed the minimum therapeutic threshold (>0.35 U/mL), the percentage of patients stabilized within the therapeutic range at 12, 24, and 48 hours, the time required to stabilization within the therapeutic range, the percentage of supratherapeutic assays (>0.67 U/mL) at 6, 12, 24, and 48 hours, the mean number of adjustments per patient to achieve stabilization within the therapeutic range, and the success rate of achieving a therapeutic assay following a dosage adjustment.

Analysis

Descriptive statistics were used to evaluate the data. Non-compliance with the nomogram was assessed by the number and severity of deviations from the nomogram. Criteria for excluding patients included any of the following: incorrect initial bolus and/or infusion rate, omission of first or subsequent heparin assays, incorrect dosage adjustment, first heparin assay drawn greater than 2 1/2 hours late or early, or any subsequent assay drawn greater than 4 hours late or 2 hours early.

Results

First Phase

During this phase, 39 patients were initiated on the nomogram. The majority were excluded from the analysis for the following reasons: 19 patients were excluded due to the temporary unavailability of the heparin assay from the hematology laboratory, 8 patients were excluded based on gross non-compliance with the nomogram, 4 patients were excluded based on obesity, and 1 patient was

excluded due to the unavailability of the chart. The remaining 7 patients, all cardiology patients, were included in the initial analysis.

The mean duration of heparin therapy for these 7 patients was 75.2 ± 91.4 hours (range 22.3-278.6 hours). Only 2 patients (28.6%) were within the therapeutic range at 24 hours and thus attained the primary outcome. At 6, 12, and 48 hours, the percentages of patients within the therapeutic range were 14.3%, 14.3%, and 66.7%, respectively. The remaining patients had supratherapeutic assays at these times. Overall, 40 heparin assays were performed. Of these assays, 27.5% were therapeutic and 65% were supra-therapeutic.

Time to exceed the therapeutic threshold was 6.4 ± 1.4 hours (range 3.8- 8.3 hours). Three patients remained supratherapeutic for the duration of heparin therapy and thus never reached the therapeutic range. Of the 4 remaining patients who did achieve the therapeutic range, they did so with a mean time of 21.2 ± 17.4 hours (range 3.8-44.7 hours). Only 1 patient was stabilized within the therapeutic range, with a time to stabilization of 41.7 hours. Length of heparin therapy in this patient was 278.6 hours.

One patient experienced a large hematoma on the left flank on the third day of heparin therapy with a drop in hemoglobin of 53 g/L, necessitating discontinuation of heparin therapy. This patient had also received treatment with alteplase on arrival to the hospital. The first two heparin assays were greater than 0.8 U/mL.

Based on these results, it was decided that the nomogram should be modified and made less aggressive. The revised nomogram retained the same heparin loading dose formula, however the initial maintenance dose infusion rates were decreased. (Figure 1) Furthermore, the second phase of the study was limited to cardiology patients with acute coronary syndromes since very few venous thrombosis patients were being treated with unfractionated heparin.

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Second Phase

The nomogram used in the second phase of the study is shown in Appendix 1.

Forty-four patients were initiated on the nomogram over approximately a one month period during the second phase of the study. In total, 25 patients had to be excluded from the data analysis for the following reasons: obesity (8), duration of heparin therapy less than 24 hours (5), indication for heparin other than coronary thrombosis (2), already receiving heparin (2), and marked non-compliance with the nomogram (16). Some patients may have been excluded based on more than one criteria. Data for remaining 19 patients were used to assess the efficacy of the nomogram (Table 1). Characteristics of these patients are presented in Table 1. A total of 95 assays was reported by the hematology laboratory. Of these, 47 (49.5%), 41 (43.2%), and 7 (7.4%) assays were therapeutic, supratherapeutic, and subtherapeutic, respectively.

The primary outcome, the percentage of patients whose assay results fell within the therapeutic range (0.35-0.67 U/mL) at 24 hours, was 36.8% (Table 2). The percentage of patients whose assay results were therapeutic at 6, 12, and 48 hours was 15.8%, 21.1%, and 83.3%, respectively. The percentage of patients whose assays were supratherapeutic at 6, 12, 24, and 48 hours was 84.2%, 78.9%, 57.9%, and 8.3%, respectively (Table 2). Table 3 further outlines the degree to which the assays were supratherapeutic. The magnitude of elevation of the supratherapeutic assays tended to diminish with time. The mean duration of heparin therapy was 60.1 +/- 19.2 hours (range 25.6-97.3).

Time to exceed the therapeutic threshold and to obtain the therapeutic range were 6.2 +/- 0.8 hours (range 5.3-8.0) and 23.0 +/- 10.0 hours (range 5.4-35.5), respectively. The mean number of dose adjustments required to achieve the first therapeutic assay was 2.1 +/- 1.3 (range 0-4). In total, 15 patients had assay results stabilized within the therapeutic range. The percentage of patients whose assay results stabilized within the therapeutic range by 12, 24, and 48 hours was 5.3%, 26.3%, and 75%, respectively (Table 3). The mean number of dosage adjustments required to achieve stabilization was 2.2 +/- 0.8 (range 0-4). The mean time to stabilization

Table 1. Patient characteristics during the second phase of the study.

*Data presented as mean +/- standard deviation, range in parentheses.

Age (y)*	
Male	64.6 +/- 11.3 (44-80)
Female	75.4 +/- 8.2 (67-89)
Sex	
Male	10
Female	9
Weight (kg)	
Male	76.3 (65-94)
Female	57.7 (41-73)
Reason for initiation of heparin:	
Unstable angina	8
Acute myocardial infarction	11
Risk factors for a major bleed:	
0	2
1	10
2	6
3	1
Location of initiation of heparin:	
ED	14
ICU/CCU	5
Concomitant disease states:	
Coronary artery disease	7
Congestive heart failure	1
Prior stroke/TIA	3
Hypertension	6
Dyslipidemia	3
Peripheral vascular disease	2
Diabetes	4
Renal insufficiency	3
Anemia	1
Malignancy	3
Other	20
Baseline laboratory values*	
aPTT (s)	32 +/- 6 (25-48)
INR	1.11 +/- 0.20 (0.91-1.60)
Platelets (/L)	244 +/- 72 (117-395)
Hemoglobin (g/L)	131 +/- 15 (129-135)

within the therapeutic range was 25.0 +/- 8.6 hours (range 5.4-35.5). However, of these 15 patients, only 11 remained within the therapeutic range until heparin therapy was discontinued. Of the remaining 4 patients, 3 had subtherapeutic results while 1 had supratherapeutic results. Of the 4 patients who were never stabilized in the therapeutic range, 2 had their heparin therapy discontinued after the first therapeutic assay, 1 received heparin for 25.6 hours and had only 1 assay drawn, and the other patient was subtherapeutic following both supratherapeutic and therapeutic results.

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Table 2. Number of patients therapeutic, supratherapeutic, and subtherapeutic at 6, 12, 24, and 48 hours the during second phase of the study.

	6 hours (n=19)	12 hours (n=19)	24 hours (n=19)	48 hours (n=12)
Therapeutic (%)	3 (15.8)	4 (21.1)	7 (36.8)	10 (83.3)
Supratherapeutic (%)	16 (84.2)	15 (78.9)	11 (57.9)	1 (8.3)
Subtherapeutic (%)	0	0	1 (5.3)	1 (8.3)

The success rate of achieving a therapeutic assay following one dosage adjustment was 43.2%. In the 16 patients who were not therapeutic at 6 hrs (all were supratherapeutic), the first dosage adjustment was successful in 3, leading to a subsequent therapeutic heparin assay. The remaining 81.2% of assays remained supratherapeutic after dosage adjustment.

There were no major bleeds among the patients included in the data analysis. However, 8 patients experienced minor bleeds and/or bruising, including the 5 patients who had received treatment with alteplase (tPA). These 5 patients had at least one other risk factor for a bleed (e.g. daily ASA). One chronic ASA user also had an initial INR of 1.53. The remaining 3 patients who had not received tPA had also had at least one risk factor for a bleed (daily ASA +/- initial INR > 1.2). Types of bleeds included: rectal bleed (1 patient), epistaxis (2 patients), and bleeding at new/old intravenous site (3 patients). There were no reports of heparin-induced thrombocytopenia.

Complete compliance with the nomogram was achieved in 5 patients. In the remaining 14 patients, a total of 27 minor deviations occurred.

Discussion

The nomogram used in the first phase of the study was successful in rapidly exceeding the therapeutic threshold. However, there was a high percentage of supratherapeutic assays, and not all patients reached the therapeutic range. Nonetheless, the results from this small patient sample were valuable as they indicated that the nomogram to be used in the second phase should be made less aggressive.

The modified nomogram used in the second phase of the study proved to be effective in rapidly and

safely exceeding the therapeutic threshold as 36.8% of patients attained the primary outcome and the mean time to obtain the therapeutic range was 23.0 hours. Furthermore, the majority of patients were stabilized within the therapeutic range with a mean time of 25.0 hours. One patient was stabilized by as quickly as 5.4 hrs since the first heparin assay was drawn in the late evening, approximately 7 hours before the daily heparin assay, drawn in the early morning.

In general, patients in the second phase tended to be supra-therapeutic with the first 1 to 3 assays before achieving the therapeutic range. The percentage of patients supra-therapeutic at 24 hours was 57.9%. Despite these results, there was no evidence of any major bleeds. In fact, studies involving patients with venous thrombosis have not clearly demonstrated that excessive anticoagulation with heparin during the first few days of therapy is associated with an increased risk of bleeding.¹⁵ However, there is sufficient proof that serious bleeding may result despite therapeutic anticoagulation with heparin.¹⁶ In the first phase of the study, 1 patient experienced a major bleed. However, this patient had also received treatment with alteplase which may have been contributory. Despite the many supra-therapeutic assays and the concomitant use of alteplase in 5 patients, there were no major bleeds associated with the modified nomogram used in the second phase.

In one study which examined the use of an aPTT-based heparin nomogram in coronary patients, 72.5% of patients had assays which were within the therapeutic range at 24 hours as compared to 36.8% of patients in the present study. (9) The discrepancy in results may be explained by the fact that the previous study made dosage adjustments based on units/kg/hour. As compared to the present study,

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this method of dosage adjustment may be more precise in achieving the therapeutic range at 24 hours. With the aPTT-based nomogram, only 72.5% exceeded the therapeutic threshold within 12 hours whereas all patients in the present study exceeded the therapeutic threshold with a mean time of 6.15 hours. Furthermore, 33% of patients in the previous study had an initial supratherapeutic aPTT as compared to 84.2% of patients in the present study. However, the present study aimed to rapidly exceed the therapeutic threshold and thus used higher loading doses which may explain this higher percentage of initially supratherapeutic assays.

In a second study which evaluated the use of an aPTT-based nomogram in a coronary care unit, the times to exceed the therapeutic threshold and to achieve a therapeutic aPTT were 6.7 hours and 20.8 hours, respectively. (10) These values are comparable to the times of 6.15 and 22.96 hours found in the present study. In contrast, at 24 hours, more patients were therapeutic and fewer were supra-therapeutic than in the present study, 51% vs. 36.8% and 38.3% vs. 57.9%, respectively. These differences may be explained by the less aggressive dosing used in the previous study, a fixed bolus of 5000 units followed by an initial infusion rate of 15 units/kg/hour.

Recently, a pharmacoeconomic study was carried out to determine the costs of monitoring unfractionated heparin therapy by the anti factor Xa assay compared to the aPTT test. (3) Although the 96-hour assay cost using the heparin assay was 16% higher than with the aPTT test, the group monitored with the heparin assay had significantly fewer tests and dosage adjustments. This reduction in the number of tests and dosage adjustments compensated for most of the increased costs associated with the assay. The investigators concluded that, given the anti-Xa heparin assay advantages over the aPTT test in certain groups of patients and the modestly increased costs, the assay should be used to monitor unfractionated heparin therapy in most large hospitals.

The present study did not consider the possible interaction between heparin and intravenous nitroglycerin, leading to decreased heparin efficacy as demonstrated by the aPTT results. This interaction is of questionable significance and if it does occur, it is

usually at higher doses of nitroglycerin. (17) Furthermore, the interaction has been reported only with the aPTT test, not with the heparin assay. Even if such an interaction occurred in our study population, the present study focused on the timeframe required to achieve the therapeutic range, rather than the exact results of the heparin assays.

Limitations of this study included the small sample size. Unfortunately, the hematology laboratory was unable to perform heparin assays for approximately two thirds of the initial phase due to a lack of reagent from the supplier. Furthermore, approximately 36% of patients initiated on the heparin nomogram during the second phase of the study had to be excluded from the data analysis due to non-compliance with the nomogram. Perfect compliance was achieved in only 5 patients. There was reluctance on the part of physicians to prescribe the recommended loading doses and initial infusion rates as dictated by the nomogram as these differed significantly from the customary 5000 unit loading dose and 1000 unit/hour maintenance infusion. In total, 7 patients were excluded based on either an incorrect loading dose, initial infusion rate, or both. The tendency also existed to make dosage adjustments based on non-therapeutic aPTT results, despite therapeutic heparin assays. Other instances of non-compliance included assays either drawn at inappropriate times or omitted altogether, inappropriate dosage adjustments or dosage adjustments not done when indicated, and missing heparin assay results. The lack of compliance may have been due to nursing time constraints and laboratory delays in providing heparin assay results. In addition, the inability of an investigator able to monitor active patients on a 24 hour basis would have played a key role in increasing compliance with the nomogram. However, it may be argued that since the evaluation of the nomogram was conducted as an effectiveness trial rather than as an efficacy trial, the low compliance rate more accurately reflects clinical practice.

Secondly, the lack of a control group does not permit any direct comparisons to be made between nomogram and empiric dosing in terms of efficacy and safety. Thirdly, this study was designed to use heparin assay results, and not patient outcomes, as endpoints. Lastly, this study examined the use of the

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nomogram in non-obese cardiology patients. Thus, extrapolation of these results to obese patients as well as to patients receiving heparin for indications other than coronary thrombosis may not be feasible. For example, as previously mentioned, patients initially presenting with deep venous thrombosis often have increased heparin requirements. Patients at increased risk of bleeding, such as stroke patients, may suffer more serious consequences if they should experience a bleed.

Positive feedback regarding the nomogram was received from both nursing and cardiology staff. Nurses appreciated the autonomy of making dosage adjustments without the need to contact cardiology staff. In turn, cardiology staff was satisfied that patients were attaining the therapeutic range and that there were no major bleeds attributed to heparin therapy. In addition, other services, including vascular surgery and family medicine, expressed interest in the nomogram. The nomogram which was implemented throughout the hospital was slightly modified. It was decided to treat a heparin assay of greater than 0.8 U/mL more aggressively by holding the infusion for 1 hour and then decreasing the rate by 250 U/hr, rather than 200 U/hr.

Conclusions

The final nomogram was successful in rapidly and safely exceeding the therapeutic threshold. Although evaluated only in cardiology patients, the use of this nomogram was implemented throughout the hospital for use in non-obese patients at low risk of bleeding presenting with either coronary or venous thrombosis.

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Appendix 1: Revised heparin nomogram used in the second phase of the study.

 The Ottawa Hospital L'Hôpital d'Ottawa			
TRIAL OF UNFRACTIONATED HEPARIN NOMOGRAM IN CARDIOLOGY PATIENTS			
IV Heparin 25,000 units in 500 mL D5W (ie; 50 units/mL)			
For use in patient at low risk of bleeding			
1. Body weight: _____ Kg			
2. Laboratory: PTT INR CBC Now Daily CBC Anti-Xa Heparin assay 6hrs after initial heparin bolus			
3. Initial heparin bolus and initial heparin infusion			
Check appropriate patient weight			
WEIGHT (kg)	INITIAL HEPARIN BOLUS (units)	Units/Hr.	INITIAL HEPARIN INFUSION (units) mL/Hr.
☐ < 60	5000	1000	20
☐ 61-70	5000	1200	24
☐ 71-80	6000	1200	24
☐ 81-90	7000	1400	28
☐ 91-100	8000	1400	28
☐ > 100	8000	1600	32
4. Dose adjustments			
HEPARIN ASSAY RESULT	HEPARIN ADJUSTMENT	NEXT HEPARIN ASSAY	
< 0.20	Repeat initial bolus, Increase 250 Units/Hr., 5 mL/Hr.	in 6 hours	
0.20-0.34	Repeat half of initial bolus, Increase 150 Units/Hr., 3 mL/Hr.	in 6 hours	
0.35-0.67	No change	next morning	
0.67-0.8	Decrease infusion by 150 Units/Hr. 3 mL/Hr.	in 6 hours	
> 0.8	Stop infusion for one hour then Decrease infusion by 200 Units/Hr., 4 mL/Hr.	in 6 hours	
Signature (physician)		Date	
PHA 21 (05/99) TRIAL		1-CHART COPY-COPIE DU DOSSIER 2-PHARMACY-PHARMACIE	

Figure 1. Revised heparin nomogram used in second phase.



**The Ottawa
Hospital** | **L'Hôpital
d'Ottawa**

TRIAL OF UNFRACTIONATED HEPARIN NOMOGRAM IN CARDIOLOGY PATIENTS

IV Heparin 25,000 units in 500 mL D5W (ie; 50 units/mL)

For use in patient at low risk of bleeding

1. Body weight: _____ Kg

2. Laboratory: PTT INR CBC Now
Daily CBC
Anti-Xa Heparin assay 6hrs after initial heparin bolus

3. Initial heparin bolus and initial heparin infusion

Check appropriate patient weight

WEIGHT (kg)	INITIAL HEPARIN BOLUS (units)	Units/Hr.	INITIAL HEPARIN INFUSION (units) mL/Hr.
☐ < 60	5000	1000	20
☐ 61-70	5000	1200	24
☐ 71-80	6000	1200	24
☐ 81-90	7000	1400	28
☐ 91-100	8000	1400	28
☐ > 100	8000	1600	32

4. Dose adjustments

HEPARIN ASSAY RESULT	HEPARIN ADJUSTMENT	NEXT HEPARIN ASSAY
< 0.20	Repeat initial bolus, Increase 250 Units/Hr., 5 mL/Hr.	in 6 hours
0.20-0.34	Repeat half of initial bolus, Increase 150 Units/Hr., 3 mL/Hr.	in 6 hours
0.35-0.67	No change	next morning
0.67-0.9	Decrease infusion by 150 Units/Hr. 3 mL/Hr.	in 6 hours

0.67-0.8

Decrease infusion by 150 Units/Hr. 3 mL/Hr.

in 6 hours

> 0.8

Stop infusion for one hour then
Decrease infusion by 200 Units/Hr., 4 mL/Hr.

in 6 hours

Signature (physician)

Date

PHA 21 (05/99) TRIAL

1-CHART COPY-COPIE DU DOSSIER

2-PHARMACY-PHARMACIE

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;1;200-203.

Enoxaparin for patients with acute coronary syndrome: Low weight and low cost?

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Original Citation

O'Brien BJ, Willan A, Blackhouse G, Goeree R, Cohen M, Goodman S. Will the use of low-molecular-weight heparin (enoxaparin) in patients with acute coronary syndrome save costs in Canada? *Am Heart J* 2000;139:423-9. [PubMed Cit](#)

Overall Study Question

The objective of this study was to determine the cost-effectiveness of treatment with unfractionated heparin compared with enoxaparin (a low molecular weight heparin) in patients who present with unstable angina and non-Q wave myocardial infarction in Canada. The authors use the data from the Canadian patients enrolled in the ESSENCE clinical trial and supplement this with Canadian cost and resource use data.(1) The one-year results of the ESSENCE trial show that enoxaparin is superior to unfractionated heparin in the primary combined endpoint of death/myocardial infarction and recurrent angina.

Are the Results of the Study Valid?

1. Did the analysis provide a full economic comparison of health care strategies?

Yes. This study provided a complete economic analysis of health care strategies. Both outcomes and costs were considered although not as transparently as in an analysis where additional money results in additional output. At first glance, it may appear to be simply a cost analysis. The research question was well defined and phrased in an answerable

format. The analysis used a relevant comparison to unfractionated heparin since use of unfractionated heparin and aspirin is the gold standard comparison for unstable angina treatment. The authors specify the viewpoint as that of the healthcare payer perspective (Ontario Ministry of Health) which is fairly broad and relevant in the context of the question posed for analysis. The outcomes considered were based on the ESSENCE study protocol which was explained in detail in the article. The ESSENCE trial showed enoxaparin to be superior to unfractionated heparin. Since the strategy was dominant (more effective and less costly), an incremental cost-effectiveness (C/E) ratio was not reported.

2. Were the costs and outcomes properly measured and valued?

Yes. The outcomes were those in the ESSENCE trial which showed enoxaparin to be superior to unfractionated heparin (i.e. efficacy data). Effectiveness data (i.e. application of the intervention into real world practice) is not available as is common to many economic analyses. Costs identified include those from the initial hospital stay (e.g. drugs, cardiac procedures, others) and at 1-year follow-up (e.g. angiograms, admissions for revascularization, angina, MI, others). The patient outcomes for the period of 30 days to 1 year were obtained by telephone follow-up of patients and their caregivers. Not all patients had 1-year follow-ups. The investigators did not measure other outpatient related costs, however these were likely small in magnitude compared to higher cost items such as hospital-based costs. Drug costs were at market value and may be higher than are available with hospital purchasing contracts. Other hospital related costs were based on the Ontario Case Costing Project (which uses microcosting) as well as a review of hospital charts for unstable angina patients with a regression analysis. The study used 1997 Canadian dollars for analysis and appropriately did not adjust for differential timing (i.e. discounting) since outcomes upon which the analysis was based occurred over a time period of less than 1 year. Since the enoxaparin was a dominant strategy, it was not appropriate to integrate costs and effects.

3. Was appropriate allowance made for uncertainties in the analysis?

Yes. A sensitivity analysis was conducted for costs such as those incurred for revascularization and admission to community hospitals. The ranges tested in the sensitivity analyses were reflective of plausible ranges related to the study question. The consequences were not varied and this is a limitation of the analysis. Statistical significance was calculated since the economic analysis was based on data from a randomized controlled trial. However, the power of the economic analysis to show a statistical difference was limited by the size of the Canadian subgroup.

4. Are estimates of costs and outcomes related to the baseline risk in the treatment population?

No. The study did not conduct a subgroup analysis related to the patient baseline risk level. This would have been possible with potential analyses including age and presentation diagnosis (myocardial infarction vs. angina). Subgroup analyses such as

these are usually conducted when there is an increased cost per effect to define the group with the best cost-effectiveness (C/E) ratio. Since the enoxaparin strategy was dominant in this analysis, this type of subgroup analysis would be less important for choosing patients who would benefit from the therapy the most, and subsequently have the lowest C/E ratio.

What are the Results?

1. What were the incremental costs and outcomes of each strategy?

Initial hospital-based costs were: cost for enoxaparin \$101.00 per patient, cost for heparin \$39.00 per patient. Revascularization costs for patients given enoxaparin \$8531.00. Revascularization costs for patients given heparin \$9099.00. Treatment with enoxaparin resulted in an initial cost savings in hospital of \$743.00 (\$10,666 vs. \$9,920; $p=0.14$). 1-Year follow-up costs were: cost for enoxaparin patients \$5,092 vs. heparin patients \$5,833 ($p=0.26$). Total costs were: enoxaparin \$15,012, heparin: \$16,497. Cost savings with enoxaparin were: \$1,485 (CI \$-93 to \$3,167; $p=0.06$).

2. Do incremental costs and outcomes differ between sub-groups?

Not applicable.

3. How much does allowance for uncertainty change the results?

The range of cost savings with the use of enoxaparin was from \$1,075 to \$1,523. One-way sensitivity analysis based on costs of various resources did not change the results and the conclusion that enoxaparin was cost saving. In the statistical analysis, the 95% CI crossed zero indicating a lack of statistically significant difference in costs between the enoxaparin and unfractionated heparin groups. However, the C/E study was not powered to show a difference since it was not the primary outcome of the ESSENCE study. Bootstrapping was used to estimate confidence intervals.

Will the results help me in caring for my patients?

1. Are the treatment benefits worth the harms and costs?

Yes. The strong dominance of treatment with enoxaparin as compared with unfractionated heparin for patients with unstable angina/non-Q-wave MI indicates that enoxaparin use can save money both during the hospital stay and for 1-year of follow-up in addition to providing improved clinical efficacy. However, the present study did not consider indirect costs, quality of life, or adverse effects such as bleeding unless this event resulting in a hospital admission. Therefore, the effects and costs of these outcomes are unknown, but are not likely significant.

2. Could my patients expect similar health outcomes?

The patients included in the ESSENCE trial were considered high risk with a history of coronary artery disease and presentation within 24 hours of having angina. Referring to the inclusion/exclusion criteria of the ESSENCE study to make comparisons to our own unstable angina patient populations, we note that the ESSENCE patients were quite typical unstable angina patients. In order to interpret the economic analysis, the reader must examine their local clinical practice patterns and compare them to those in the ESSENCE study. The efficacy data used by the investigators included 1-year outcomes, representing a sufficient length of patient follow-up.

3. Could I expect similar costs?

Yes, in general. Costs are outlined in Table IV of the original paper. The authors used 1-year costs from Ontario. Costs may be different in other hospitals and in other areas of Canada, however these costs these values generally represent a more appropriate and accurate estimate of Canadian resource use and cost per unit than economic analyses conducted in other countries. Resource consumption may be different than in general practice since patients were enrolled in ESSENCE and may have had protocol-specific costs. However, these costs should balance out between the unfractionated heparin and the enoxaparin groups. A previously conducted Canadian economic analysis of enoxaparin in this setting has been published by Balen et al. (2) These investigators considered 30-day outcomes only, and the study involved fewer patient numbers. The study yielded some similar costs (i.e. heparin \$31 vs. \$39, enoxaparin \$82 vs. \$101), while others differed significantly. Despite these disparities, the previous investigators found similar results (i.e. enoxaparin was the dominant strategy), demonstrating consistency and robustness of the results.

How can the results be put into the context of previous knowledge and clinical practice? What are any important methodological issues with the study? How should the study findings be applied to the field of clinical pharmacotherapy?

The results of this economic analysis are consistent with those of Balen and colleagues in Canada in addition to economic analyses conducted in France, Britain and the United States, demonstrating a consistent conclusion that the use of enoxaparin in the treatment of unstable angina/non-Q wave myocardial infarction is more effective and less costly than unfractionated heparin. (2-5) Despite the fact that the acquisition cost of enoxaparin is greater than that of unfractionated heparin, when all the costs and consequences are considered in appropriately conducted economic analyses, enoxaparin emerges as a strongly dominant option. Based on the results of this analysis, enoxaparin should become the gold standard therapy for antithrombotic therapy for patients presenting with unstable angina or non-Q wave myocardial infarction with similar characteristics as those in the ESSENCE trial.

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Enoxaparin for patients with acute coronary syndrome: Low weight and low cost?

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Reviewer's profession/specialty: Pharmacy//Cardiology/Internal Medicine

Original Citation

O'Brien BJ, Willan A, Blackhouse G, Goeree R, Cohen M, Goodman S. Will the use of low-molecular-weight heparin (enoxaparin) in patients with acute coronary syndrome save costs in Canada? *Am Heart J* 2000;139:423-9.

Overall Study Question

The objective of this study was to determine the cost-effectiveness of treatment with unfractionated heparin compared with enoxaparin (a low molecular weight heparin) in patients who present with unstable angina and non-Q wave myocardial infarction in Canada. The authors use the data from the Canadian patients enrolled in the ESSENCE clinical trial and supplement this with Canadian cost and resource use data.⁽¹⁾ The one-year results of the ESSENCE trial show that enoxaparin is superior to unfractionated heparin in the primary combined endpoint of death/myocardial infarction and recurrent angina.

Are the Results of the Study Valid?

1. Did the analysis provide a full economic comparison of health care strategies?

Yes. This study provided a complete economic analysis of health care strategies. Both outcomes and costs were considered although not as transparently as in an

analysis where additional money results in additional output. At first glance, it may appear to be simply a cost analysis. The research question was well-defined and phrased in an answerable format. The analysis used a relevant comparison to unfractionated heparin since use of unfractionated heparin and aspirin is the gold standard comparison for unstable angina treatment. The authors specify the viewpoint as that of the healthcare payer perspective (Ontario Ministry of Health) which is fairly broad and relevant in the context of the question posed for analysis. The outcomes considered were based on the ESSENCE study protocol which was explained in detail in the article. The ESSENCE trial showed enoxaparin to be superior to unfractionated heparin. Since the strategy was dominant (more effective and less costly), an incremental cost-effectiveness (C/E) ratio was not reported.

2. Were the costs and outcomes properly measured and valued?

Yes. The outcomes were those in the ESSENCE trial which showed enoxaparin to be superior to unfractionated heparin (i.e. efficacy data). Effectiveness data (i.e. application of the intervention into real world practice) is not available as is common to many economic analyses. Costs identified include those from the initial hospital stay (e.g. drugs, cardiac procedures, others) and at 1-year follow-up (e.g. angiograms, admissions for revascularization, angina, MI, others). The patient outcomes for the period of 30 days to 1 year were obtained by telephone follow-up of patients and their caregivers. Not all patients had

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1-year follow-ups. The investigators did not measure other outpatient related costs, however these were likely small in magnitude compared to higher cost items such as hospital-based costs. Drug costs were at market value and may be higher than are available with hospital purchasing contracts. Other hospital related costs were based on the Ontario Case Costing Project (which uses microcosting) as well as a review of hospital charts for unstable angina patients with a regression analysis. The study used 1997 Canadian dollars for analysis and appropriately did not adjust for differential timing (i.e. discounting) since outcomes upon which the analysis was based occurred over a time period of less than 1 year. Since the enoxaparin was a dominant strategy, it was not appropriate to integrate costs and effects.

3. Was appropriate allowance made for uncertainties in the analysis?

Yes. A sensitivity analysis was conducted for costs such as those incurred for revascularization and admission to community hospitals. The ranges tested in the sensitivity analyses were reflective of plausible ranges related to the study question. The consequences were not varied and this is a limitation of the analysis. Statistical significance was calculated since the economic analysis was based on data from a randomized controlled trial. However, the power of the economic analysis to show a statistical difference was limited by the size of the Canadian subgroup.

4. Are estimates of costs and outcomes related to the baseline risk in the treatment population?

No. The study did not conduct a subgroup analysis related to the patient baseline risk level. This would have been possible with potential analyses including age and presentation diagnosis (myocardial infarction vs. angina). Subgroup analyses such as these are usually conducted when there is an increased cost per effect to define the group with the best cost-effectiveness (C/E) ratio. Since the enoxaparin strat-

egy was dominant in this analysis, this type of subgroup analysis would be less important for choosing patients who would benefit from the therapy the most, and subsequently have the lowest C/E ratio.

What were the Results?

1. What were the incremental costs and outcomes of each strategy?

Initial hospital-based costs were: cost for enoxaparin \$101.00 per patient, cost for heparin \$39.00 per patient. Revascularization costs for patients given enoxaparin \$8531.00. Revascularization costs for patients given heparin \$9099.00. Treatment with enoxaparin resulted in an initial cost savings in hospital of \$743.00 (\$10,666 vs. \$9,920; $p=0.14$). 1-Year follow-up costs were: cost for enoxaparin patients \$5,092 vs. heparin patients \$5,833 ($p=0.26$). Total costs were: enoxaparin \$15,012, heparin: \$16,497. Cost savings with enoxaparin were: \$1,485 (CI \$-93 to \$3,167; $p=0.06$).

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Commentary

The results of this economic analysis are consistent with those of Balen and colleagues in Canada in addition to economic analyses conducted in France, Britain and the United States, demonstrating a consistent conclusion that the use of enoxaparin in the treatment of unstable angina/non-Q wave myocardial infarction is more effective and less costly than unfractionated heparin. (2-5) Despite the fact that the acquisition cost of enoxaparin is greater than that of unfractionated heparin, when all the costs and consequences are considered in appropriately conducted economic analyses, enoxaparin emerges as a strongly dominant option. Based on the results of this analysis, enoxaparin should become the gold standard therapy for antithrombotic therapy for patients presenting with unstable angina or non-Q wave myocardial infarction with similar characteristics as those in the ESSENCE trial.

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J Inform Pharmacother 2001;4:200-203.

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;4:204-207.

The addition of rosiglitazone to metformin improves glycemic control in patients with type 2 diabetes: Are things looking "ROSI'ER"?

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Reviewer's profession/specialty: Ambulatory care

Original Citation

Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. *JAMA* 2000;283:1695-702. [PubMed Cit](#)

Overall Study Question

This study was conducted to determine the effectiveness and safety of adding rosiglitazone to maximal doses of metformin in patients with inadequately controlled diabetes?

Three hundred and forty-eight patients (mean age 58 years, mean HbA1C 8.8%) who had type 2 diabetes with a fasting plasma glucose (FPG) between 7.7 and 16.7 mmol/L (mean approximately 12 mmol/L) while taking metformin 2.5 g/day, had an insulin secretory capacity (fasting C-peptide concentration) of at least 0.27 nmol/L at screening, a body mass index between 22 to 38 (mean 30.1), and a weight change of no more than 10% between screening and baseline were included in this study. Exclusion criteria included clinically significant renal or hepatic disease, angina, cardiac insufficiency (NYHA class III or IV), symptomatic diabetic neuropathy, clinically significant ECG abnormalities, abnormal laboratory results, chronic insulin use, participation in any rosiglitazone-related study, or the use of any investigational drug (with the exception of metformin) within 30 days of the study.

Patients were allocated to metformin + placebo (n=116), metformin + rosiglitazone 4 mg/day (n=119), or metformin + rosiglitazone 8 mg/day (n=113) for 26 weeks. The main outcome measures were the change in HbA1C, insulin sensitivity (HOMA-S), Beta-cell function (HOMA-B), and lipid levels. Safety was also assessed.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Randomization was computer generated in a 1:1:1 ratio.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. 348 patients were randomized and 290 completed the study. 16 patients withdrew due to lack of efficacy, 18 withdrew due to an adverse effect, and 17 withdrew for other reasons. Seven patients were lost to follow-up.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. Patients, investigators, and sponsors were blind to treatment product and allocation.

4. Were the groups similar at the start of the trial?

Yes. Baseline characteristics were similar among the treatment groups. There were slightly more men in the control group (metformin and placebo).

5. Aside from the experimental intervention, were the groups treated equally?

Yes.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

There was a dose dependent statistically significant decrease in HbA1C and FPG at week 26 in both the rosiglitazone 4 mg/day (-0.56% and -1.8 mmol/L, respectively) and rosiglitazone 8 mg/day (-0.78%, and -2.7 mmol/L, respectively) groups when compared with an increase in the control group (0.45% and 0.33 mmol/L, respectively). Thus, when compared to placebo, the HbA1C after 26 weeks of therapy was 1% and 1.2% lower in the rosiglitazone 4 mg and 8 mg groups, respectively.

There was a statistically significant increase (Absolute Risk Difference (ARD)) in the total cholesterol

(4mg, 0.53 mmol/L; 8mg, 0.60 mmol/L), HDL (4mg, 0.08 mmol/L; 8mg, 0.10mmol/L), and LDL levels (4mg, 0.36 mmol/L; 8mg 0.40 mmol/L) when both doses of rosiglitazone were compared to the control group. HOMA-S and HOMA-B values also increased in a dose-dependent manner with the addition of rosiglitazone to metformin.

Metformin plus rosiglitazone 4 mg/day, 8 mg/day or placebo for Type 2 Diabetes after 26 weeks of therapy

% of patients achieving outcome

1%
decrease- HbA1C < 8%
HgA1C
FPG-7.7mmol/L

Metformin + Placebo	7.0%	35.9%	8.9%
Metformin + Rosiglitazone 4mg/ d	32.8%	-	19.8%
Metformin + Rosiglitazone 8mg/ d	37.2%	57.3%	32.6%
NNT (Metformin + Rosiglitazone 4mg/ d)	3.9	-	9.2
NNT (Metformin + Rosiglitazone 8mg/ d)	3.3	4.7	4.2

The incidence of side effects was not different among all three treatment groups with approximately 76% of patients experiencing at least one adverse event. However, both rosiglitazone groups experienced small decreases in hemoglobin (4mg, -5.0g/L; 8mg, -8.0g/L) and hematocrit, more edema (4 mg, 2.5%; 8 mg, 3.5%; control, 0.9%) and more weight gain (control, -1.2kg; 4mg, 0.7kg; 8mg, 1.9kg) as compared to the placebo arm. No one in the rosiglitazone arms experienced a clinically significant increase in ALT (i.e. greater than 3 times the upper limit of normal) during the study. Mean changes in AST, total bilirubin, and alkaline phosphatase were not different among groups.

2. How precise was the estimate of the treatment effect?

The results are statistically significant in favour of the treatment groups when comparing treatment to control groups. Confidence intervals (CI) and standard deviations are not provided in the text. However results provided in the figures show that compared to control, the addition of rosiglitazone to metformin produces a statistically different in HgA1c ($p < 0.001$) and FPG ($p < 0.001$). The 95% confidence intervals provided on the graph examining changes in HgA1c for both rosiglitazone groups compared to control after 26 weeks of therapy demonstrate that even the lower ends of the 95% CI show that a minimal clinically important difference in HgA1c has occurred for both rosiglitazone groups compared with the control group (lower ends of the 95% CI shows approximately a 0.65% reduction (4 mg) and 0.8% reduction (8 mg) in HgA1c).

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. The patients in this study were obese patients with Type 2 diabetes who had high FPG despite monotherapy with metformin. This patient population is very representative of patients with type 2 diabetes.

2. Were all clinically important outcomes considered?

No. Surrogate endpoints were measured in this study. There were no long term macrovascular or microvascular outcomes considered.

3. Are the likely treatment benefits worth the potential harms and costs?

Yes. Improving blood glucose control (with drug monotherapy) even by a reduction in HgA1c of 0.9% can reduce the risk of any diabetes related endpoint (including microvascular and macrovascular endpoints) by 12% relative to diet therapy alone (NNT =20). (1) The adverse effects associated with rosiglitazone (edema, weight gain, headache, reduction in hemoglobin, upper respiratory tract infections, and increases in LDL and cholesterol) can be detected with careful monitoring and therefore dealt with if they prove to be bothersome or clinically detrimental to the patient.

Commentary

With the introduction of the new thiazolidinediones to the market, there are more options available for the treatment of type 2 diabetes. In the UKPDS trial the investigators demonstrated that, despite intensive treatment, monotherapy often failed to maintain optimal glycemic control. (1) Many patients (39%) required the addition of insulin or metformin to maintain control. The results of the current study and the study by Wolffenbuttal and colleagues (involving rosiglitazone in combination with sulphonylureas) suggests that rosiglitazone can improve glycemic control when used in combination therapy in patients who have experienced secondary failure to one oral hypoglycemic agent. (2) However, the question remains as to whether these agents are equally or more effective than the current standard therapy (metformin plus a sulphonylurea). (3)

It is interesting to examine the effects of the combination of a sulphonylurea plus metformin versus metformin alone. In one trial, 22% of patients on combination therapy achieved a FPG of 7.7 mmol/L or less, compared to 3% in the metformin monotherapy group after 29 weeks of treatment. (4) Although direct comparisons cannot be made between these results and the results from Fonseca et al, it may be hypothesized that the effects would be similar between the two combinations (i.e. metformin + sulphonylurea vs. metformin + rosiglitazone). To date, there have been no trials comparing the effects of the combination of metformin and a sulphonylurea versus the combination of a thiazolidinedione and either metformin or a sulphonylurea. Another question that remains is whether patients who have failed therapy with a combination of metformin and a sulphonylurea would benefit from the addition of a

thiazolidinedione. Further investigations need to be performed to assess whether rosiglitazone (and its counterpart pioglitazone) have a more extensive place in therapy.

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Reviewer's profession/specialty: Ambulatory care

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Yes. The patients in this study were obese patients with Type 2 diabetes who had high FPG despite monotherapy with metformin. This patient population is very representative of patients with type 2 diabetes.

2. Were all clinically important outcomes considered?

No. Surrogate endpoints were measured in this study. There were no long term macrovascular or microvascular outcomes considered.

3. Are the likely treatment benefits worth the potential harms and costs?

Yes. Improving blood glucose control (with drug monotherapy) even by a reduction in HgA1c of 0.9% can reduce the risk of any diabetes related endpoint (including microvascular and macrovascular endpoints) by 12% relative to diet therapy alone (NNT = 20). (1)

The adverse effects associated with rosiglitazone (edema, weight gain, headache, reduction in hemoglobin, upper respiratory tract infections, and increases in LDL and cholesterol) can be detected with careful monitoring and therefore dealt with if they prove to be bothersome or clinically detrimental to the patient.

Commentary

With the introduction of the new thiazolidinediones to the market, there are more options available for the treatment of type 2 diabetes. In the UKPDS trial the investigators demonstrated that, despite intensive treatment, monotherapy often failed to maintain optimal glycemic control. (1) Many patients (39%) required the addition of insulin or metformin to maintain control. The results of the current study and the study by Wolffenbuttal and colleagues (involving rosiglitazone in combination with sulphonylureas) suggests that rosiglitazone can improve glycemic control when used in combination therapy in patients who have experienced secondary failure to one oral hypoglycemic agent. (2) However, the question remains as to whether these agents are equally or more effective than the current standard therapy (metformin plus a sulphonylurea). (3)

It is interesting to examine the effects of the combination of a sulphonylurea plus metformin versus metformin alone. In one trial, 22% of patients on combination therapy achieved a FPG of 7.7 mmol/L or less, compared to 3% in the metformin monotherapy group after 29 weeks of treatment. (4) Although direct comparisons cannot be made between these results and the results from Fonseca et al, it may be hypothesized that the effects would be similar between the two combinations (i.e. metformin + sulphonylurea vs. metformin + rosiglitazone). To date, there have been no trials comparing the effects of the combination of metformin and a sulphonylurea versus the combination of a thiazolidinedione and either metformin or a sulphonylurea. Another question that remains is whether patients who have failed therapy with a combination of metformin and a sulphonylurea would benefit from the addition of a thiazolidinedione. Further investiga-

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tions need to be performed to assess whether rosiglitazone (and its counterpart pioglitazone) have a more extensive place in therapy.

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J Inform Pharmacother 2001;4:204-207.

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;4:208-210.

Filgrastim for the treatment of hospitalized patients with multilobar pneumonia; can it "stimulate" an improved response?

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Reviewer: Tania Mysak, BSP, PharmD

Reviewer's email address: mysak@interchange.ubc.ca

Reviewer's profession/specialty: Pharmacy/Acute Care

Original Citation

Nelson S, Heyder AM, Stone J, Bergeron MG, Daugherty S, Peterson G et al. A randomized controlled trial of filgrastim for the treatment of hospitalized patients with multilobar pneumonia. J Infect Dis 2000;182:970-3. [PubMed Cit](#)

Overall Study Question

To assess whether filgrastim (r-metHuG-CSF [recombinant human methionine granulocyte colony-stimulating-factor]) is superior to placebo in decreasing the therapeutic failure rate in patients with multilobar community-acquired pneumonia. Four hundred eighty (480) hospitalized adults (≥ 18 years old) receiving antibiotics for multilobar community-acquired pneumonia were randomized to receive either filgrastim or placebo in addition to their standard antibiotic therapy. Study drug was started within 24 hours of hospitalization and continued for ≤ 10 days, or until white blood cell (WBC) count reached $> 75 \times 10^9/L$, IV antibiotics were discontinued, or patient was discharged from hospital. The primary endpoint was the incidence of therapeutic failure through day 29. Therapeutic failure was defined as development of organ dysfunction (ARDS, DIC, acute renal failure, or shock), empyema, or death from any cause. Secondary outcomes included mortality at 28 days, number of days in ICU, time to stability or improvement as demonstrated on chest radiograph, and incidence of chest radiograph resolution. Safety endpoints were adverse events and clinical laboratory abnormalities.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Patients were randomized to receive filgrastim or placebo.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. Sixteen (3%) of patients did not finish the study for various reasons (patient request, administrative decision, or loss to follow-up). Withdrawals for each respective reason were balanced across the groups. The authors stated that the primary endpoint was analyzed on an intention-to-treat basis, while the analysis of secondary outcomes were based on an evaluable subset of subjects who met all eligibility criteria and received ≥ 3 doses of study drug.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

The methods section suggests that this study was double-blinded, however, details of this blinding are not provided. The only detail provided is that the manufacturer provided the study drug and vehicle (to act as placebo) in identical vials. Although the primary care provider making daily care decisions may have been blinded, we do not know if persons evaluating the chest radiographs or determining the degree of organ dysfunction were blinded, which could potentially result in bias.

4. Were the groups similar at the start of the trial?

Yes. Baseline demographic characteristics were similar across the groups, and baseline disease characteristics were similar.

5. Aside from the experimental intervention, were the groups treated equally?

Aside from the intervention, patient supportive care and monitoring (concomitant medications, microbiologic cultures etc.) were allowed as medically indicated. Assuming the primary care provider was blinded, the groups were most likely treated similarly.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

The incidence of patients experiencing therapeutic failure through day 29 was 42 (17.3%) in the placebo group versus 40 (16.9%) in the filgrastim group. The difference between

the groups was not statistically significant in the intent-to-treat analysis, nor the evaluable subset analysis. This study was adequately powered, and sufficient patients recruited, to detect an absolute decrease in the proportion of treatment failures of approximately 50%, although no alpha and beta values for this calculation were provided. As well, no statistically significant effect of treatment was seen in any of the secondary endpoints or safety endpoints.

2. How precise was the estimate of the treatment effect?

No treatment effect was demonstrated and confidence intervals were not reported.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. Although no treatment effect was noted, the patients enrolled in the study are representative of patients with multilobar community-acquired pneumonia. As well, this study appears to confirm the results of a similar study done by these authors in which filgrastim was not superior to placebo in terms of time to resolution of morbidity, mortality, or length of stay in hospital.

2. Were all clinically important outcomes considered?

Yes.

3. Are the likely treatment benefits worth the potential harms and costs?

Filgrastim was not shown to be superior to placebo in decreasing the incidence of therapeutic failure, morbidity, or mortality in patients with multilobar community-acquired pneumonia. Therefore, it is unlikely that a treatment “benefit” would outweigh any potential risks.

Commentary

The premise behind this study is that endogenous granulocyte colony-stimulating factor concentrations are increased in a variety of infectious disease states, suggesting an important role for this growth factor in these circumstances. As animal models of infection have indicated filgrastim can augment host response, and filgrastim has been shown to be well tolerated in humans for other indications (non-neutropenic diabetic foot infections), the authors decided to investigate whether filgrastim would be of benefit in patients with severe pneumonia. Amgen (manufacturer of filgrastim) has now funded several studies to this effect, both with safety endpoints (Phase 1) and clinical endpoints (Phase 3). Although filgrastim appears to be well tolerated, any treatment benefit has not been demonstrated. At this time, recommending filgrastim for this patient population is not warranted.

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J Inform Pharmacother 2001;4:208-210.

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2000;4:211-213.

Vaso peptide Inhibition for Congestive Heart Failure: Are You IMPRESS'ed?

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Reviewer's email address: shalansk@interchange.ubc.ca

Reviewer's profession/specialty: Cardiology/Research

Original Citation

Rouleau JL, Pfeffer MA, Stewart DJ, Isaac D, Sestier F, Kerut EK, et al. for the IMPRESS investigators. Comparison of vaso peptide inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure: IMPRESS randomised trial. Lancet 2000;356:615-20. [PubMed Cit](#)

Overall Study Question

Omapatrilat is the first vaso peptide inhibitor being studied for hypertension and heart failure. This class of drugs inhibits both angiotensin converting enzyme (ACE), and neutral endopeptidase (NEP) which metabolizes endogenous vasodilator peptides. Animal studies suggest that, compared to ACE inhibitors, the dual mechanism of action of vaso peptide inhibitors may better correct the imbalance between endogenous vaso constrictors and vasodilators in congestive heart failure (CHF). (1). The primary objective of the IMPRESS trial was to compare the effects of omapatrilat with those of lisinopril on exercise tolerance in patients with congestive heart failure (CHF) after 12 weeks of therapy. Secondary endpoints included exercise tolerance at 24 weeks, adverse events, death, and comorbid events for worsening heart failure (hospital admission, discontinuation of study treatment). On study entry, patients had stable (>3 months) symptomatic heart failure (NYHA II-IV), decreased left-ventricular ejection fraction, and were receiving a stable (>4 weeks) dose of ACE inhibitors.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Patients qualified for this study through a series of exercise tolerance tests, first

while taking baseline medications (which had to include an ACE inhibitor) and then placebo. If all entry criteria were met, ACE inhibitor treatment was stopped and patients were randomized the next day to omapatrilat or lisinopril. Omapatrilat was initiated at an oral dose of 10mg once daily with a target dose of 40mg daily; lisinopril was initiated at an oral dose of 5mg once daily with a target dose of 20mg daily. The doses were force-titrated to target or maximum tolerated dose at weekly intervals for up to 3 weeks.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Seven hundred and sixteen patients were enrolled, but 143 were considered ineligible or withdrew before randomization. This left 289 patients assigned to omapatrilat and 284 assigned to lisinopril. Twenty-four patients withdrew from each arm (21 omapatrilat and 16 lisinopril patients due to adverse events), while 7 omapatrilat and 10 lisinopril patients died before study completion. Therefore, 258 omapatrilat and 250 lisinopril patients completed the study protocol. These results are clearly outlined in a figure in the original publication. The investigators identify that analysis of the primary outcome was done by intention to treat, however 12-week exercise tolerance tests (ETT) results are reported for fewer patients than were assigned to each treatment arm (274 versus 289 for omapatrilat, and 265 versus 284 for lisinopril). Although no explanation is provided in the text of the article, it may be assumed that the difference in these numbers is attributed to patients who did not complete study treatment and failed to return for follow-up ETT.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Although the abstract states the study was "double-blind", no details of the blinding procedure are outlined in the original publication.

4. Were the groups similar at the start of the trial?

Yes. Baseline and demographic variables were similar between the two treatment groups including gender, ethnic origin, age, severity and cause of CHF, laboratory and hemodynamic measurement, and concomitant medications. However, there were slightly more patients in the lisinopril group taking long-acting nitrates (32% versus 27%) and calcium-channel blockers (4% versus 2%).

5. Aside from the experimental intervention, were the groups treated equally?

There is no information in the original publication to suggest that the two study groups were treated differently.

6. Overall, are the results of the study valid?

Yes. Unfortunately, however, much media attention has focused on the secondary endpoints (e.g. composite of death, hospitalization, and discontinuation of study treatment due to worsening heart failure) which cannot be considered definitive.

What were the Results?

1. How large was the treatment effect?

The adjusted mean change from baseline in exercise duration at 12 weeks was 24 seconds for the omapatrilat group and 31 seconds for the lisinopril group ($p=0.45$). The difference at 24 weeks was also not statistically significant. There was no significant difference between the treatment groups with respect to total number of adverse events (25% for omapatrilat versus 33% for lisinopril) or total number of patients experiencing at least one adverse event (15% for omapatrilat versus 21% for lisinopril). However, more patients in the lisinopril group experienced cardiovascular side effects and elevated creatinine, while more patients in the omapatrilat group experienced dizziness, vision disturbance, diarrhea, and tracheobronchitis. One patient receiving lisinopril and none of the omapatrilat patients experienced angioedema (see Commentary for a discussion of angioedema).

In terms of clinical outcomes (all were secondary endpoints), there was no statistically significant difference in death from any cause (2% for omapatrilat versus 4% for lisinopril). There was a non-significant difference in the composite of death or admission for worsening heart failure favouring omapatrilat (5% versus 9%, $p=0.052$) and a significant difference in the composite of death, admission or discontinuation of study treatment favouring omapatrilat (6% versus 10%, $p=0.035$). Assessment of NYHA functional class suggested omapatrilat had more benefit in patients with more severe CHF (NYHA class III or IV).

2. How precise was the estimate of the treatment effect?

The only reported measurement of precision relevant to the primary outcome was standard error of the mean for change from baseline exercise duration (6 seconds for both treatment groups). For the secondary outcomes, the hazard ratio for the composite of death or admission was 0.52 (95% CI 0.27-1.02) and for the composite of death, admission or study treatment discontinuation was 0.52 (95% CI 0.28-0.96).

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Since omapatrilat is not available in Canada or the U.S., these results cannot currently be applied to North American patients. The relatively small size of this trial and the use of a surrogate endpoint as the primary outcome make it difficult to draw conclusions regarding the potential place of omapatrilat in the treatment CHF. The results of large ongoing studies in CHF

and hypertensive patients will better define the place of vasoepitidase inhibitors if approved for use in North America (see Commentary).

2. Were all clinically important outcomes considered?

Yes, but not as the primary outcome.

3. Are the likely treatment benefits worth the potential harms and costs?

Since omapatrilat is not currently marketed in North America, the cost of therapy is unknown. Potential harm seems limited based on the results of this trial, however the new drug application for omapatrilat was voluntarily withdrawn in April 2000 when the FDA raised concern over the incidence of angioedema in the pre-approval database. There were 44 cases in over 6000 patients, four of which required intubation. This is thought to be higher than the incidence for ACE inhibitors over a comparable treatment duration. (2)

Commentary

The IMPRESS trial results are not definitive, but provide evidence to support further research assessing the risk versus benefit of vasoepitidase inhibition. Since vasoepitidase inhibitors likely increase bradykinin levels more than ACE inhibitors, it is logical that they could lead to a higher incidence of angioedema (1, 3). However, this mechanism may also result in added clinical benefit. The results of several large ongoing trials will be key in determining the fate of omapatrilat in the treatment of CHF and hypertension. Bristol Myers Squibb (BMS), the developers of omapatrilat, launched the Omapatrilat Cardiovascular Treatment Assess Versus Enalapril (OCTAVE) trial at least in part to address the concerns of the FDA. The investigators plan to include 25,000 hypertension patients in 5000 clinical centers, and hope the results will be available in Spring 2001. In addition, a large trial in CHF, Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE), is ongoing and expects to report results in 2002 (4). A meta-analysis including data from IMPRESS and an unpublished safety study (a total of 1242 patients) was presented in March 2000 at the American College of Cardiology meeting. The results suggest a significant reduction in the composite of death and CHF hospitalization compared to lisinopril (RR 0.72, 95% CI 0.53-0.97, p=0.03). However, approval of omapatrilat in Canada and the U.S. likely hinges on the efficacy and safety data which will be available from OCTAVE.

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Reviewer's profession/specialty: Cardiology/Research

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J Inform Pharmacother 2001;4:211-213.

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;4:214-217.

The safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia: Are all formulations created equal?

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Original Citation

Wingard J, White MH, Anaissie E, Raffalli J, Goodman J, Arrieta A et al. A randomized double blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. *Clin Infect Dis* 2000;31:1155-1163 [PubMed Cit](#)

Overall Study Question

To determine the frequency of infusion-related reactions, nephrotoxicity and other safety parameters of amphotericin B lipid complex (ABLC) and two dose regimens of liposomal amphotericin B for empiric treatment of febrile neutropenic patients at risk for fungal infections.

Design: A randomized, double-blinded, multicenter (18 centers) trial. **Patients:** Subjects aged ≥ 2 years old who were neutropenic (ANC < 500 cells/mm³) were enrolled in the study if investigators suspected a fungal infection, as demonstrated by fever after at least 72 h of broad-spectrum antibacterial therapy. Subjects were excluded from the study if they had liver disease (transaminase levels > 10 times the upper limits of normal or a total bilirubin or alkaline phosphatase level > 5 times the upper limit of normal), serum creatinine level > 3 mg/dL, uncontrolled bacteremia, received greater than two doses of systemic amphotericin B or preparations containing amphotericin B within the previous 10 days, had an anticipated survival of less than 2 weeks or had clinical evidence indicating a deep or disseminated fungal infection. **Intervention:** Patients were randomized to receive ABLC 5mg/kg/d or liposomal amphotericin 5mg/kg/d or 3mg/kg/d through central venous catheter over 2 hours. Treatment continued until the patient's ANC was ≥ 500 cells/mm³ or for up to 3 days after neutrophil recovery, to a maximum of 42 days. Administration of premedications prior to the first administration of medication was prohibited. After the first day, the clinician was allowed the option of prescribing premedications if

a reaction to the first dose of a study drug occurred. Saline loading was used according to standard practices at each center. Endpoints: The primary endpoint was the incidence of chills/rigors on day 1. Other outcome variables included the overall frequency infusion-related reactions (i.e., fever, nausea, vomiting, pain, hypertension, tachycardia, chest pain, vasodilation and hypotension), the incidence of medication use to treat infusion-related reactions (i.e. acetaminophen, meperidine, diphenhydramine, and hydrocortisone), nephrotoxicity (increase in serum creatinine >100% baseline), hypokalemia (potassium <3 mEq/L), anemia (hemoglobin <8 g/dL), and hepatotoxicity. The investigators also assessed clinical efficacy, although the study was not powered to evaluate this particular outcome.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Patients were first stratified as "high risk" or "low risk" on the basis of use or nonuse of nephrotoxic immunosuppressants (i.e., cyclosporine or tacrolimus). Patients were then randomized to receive either ABLC, high or low dose liposomal amphotericin (1:1:1 randomization).

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. All patients were accounted for and an intention-to-treat analysis was used. Three hundred and forty-two patients underwent screening evaluation and 250 patients met the inclusion criteria. Of these, 6 patients did not receive study drug for administrative reasons, thus a total of 244 patients who were randomized into the study were analyzed.

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Yes. The patient, investigator and study coordinators were blinded as to the treatment administered. When pharmacy staff prepared the study drug, they provided a blinded label and covered each dose with an opaque bag due to differences in colour and opacity of each agent. IV tubing was not masked, as visible differences between drugs were not discernable.

4. Were the groups similar at the start of the trial?

Yes. Baseline demographic, disease and other characteristics were similar across the groups.

5. Aside from the experimental intervention, were the groups treated equally?

Yes. Aside from the premedication after day 1 and saline loading that was allowed as medically indicated. However, since the primary care provider was blinded, the groups were most likely treated similarly.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

Infusion-related reactions

The incidence of chills/rigors on day 1 was lower among patients administered liposomal amphotericin (3mg/kg 18.8% and 5mg/kg 23.5%) than in the ABLC group (79.5%, $p<0.001$). In addition, the overall frequency infusion-related reactions on day 1 were also lower in the two liposomal amphotericin groups (3mg/kg 51.8% and 5mg/kg 48.1%) compared to ABLC (88.5%, $p<0.001$). The lower incidence of reactions in the liposomal amphotericin arm was observed even after adjustment for age, sex, receipt of a bone marrow transplant, transplant type, or the use of immunosuppressants. In addition, the number of medications used to treat infusion-related reactions was also lower in the liposomal amphotericin groups (3-mg/kg 43.5% and 5-mg/kg 37.0%) compared to ABLC (73.1%, $p<0.001$).

On days 2 to 5, when premedications for the prevention of infusion-related reactions were allowed, the incidence of infusion-related chills and the overall frequency of infusion-related reactions were lower in the ABLC group, but unchanged for the two liposomal amphotericin groups. The difference in the incidence of chills/rigors remained statistically significant in both liposomal amphotericin groups (3-mg/kg 21.0% and 5-mg/kg 24.3%) when compared to the ABLC group (50.7%, $p<0.001$). However, only the 5-mg/kg liposomal amphotericin and ABLC groups were different in terms of the incidence of overall frequency of infusion-related reactions ($p=0.009$).

Nephrotoxicity

Significantly less nephrotoxicity was observed in the liposomal amphotericin groups (3mg/kg 14.1%, 5mg/kg 14.8%) as compared to those the ABLC group (42.3%, $p<0.001$). This relationship persisted regardless of age, receipt of a bone marrow transplant, transplant type, or use of immunosuppressants. A peak creatinine value >2.5 mg/dL occurred in 7.1% of the 3-mg/kg liposomal amphotericin group, 3.7% of the 5-mg/kg liposomal amphotericin group, and 17.9% of the ABLC group ($p=0.01$).

When rates of nephrotoxicity were evaluated by patient-risk strata, there were no statistical differences between the 3 treatment groups, in either the high or low risk strata although there was a trend toward higher nephrotoxicity in the high-risk stratum than in the low-risk stratum for the 5-mg/kg liposomal amphotericin group (36.4% vs. 11.4%; $p=0.053$). However, there were no statistical differences between high- and low-

risk patients in the 3-mg/kg liposomal amphotericin group (15.4% vs. 13.9%) or the ABLC group (45.5% vs. 41.8%).

When patients were divided into 3 age groups (<16 years, 16-40 years, and >40 years), there was no association between age and any of the nephrotoxicity end points for the two liposomal amphotericin groups. For the ABLC cohort there were no differences by age with regard to doubling of creatinine value, but there was a nonsignificant trend toward higher peak creatinine values at the 2.0, 2.5, and 3.0 mg/dL end points for older individuals in this group.

Hepatotoxicity, hypokalemia, and anemia

There were no statistically significant differences between the treatment groups with respect to hepatotoxicity, which occurred in 11.5% of all patients. [Note: The authors identify that no adjustments were made for multiple comparisons, however the p value was adjusted to $p \leq 0.01$ to avoid chance differences.] Although there was no difference in frequency of hypokalemia between patients who received 5mg/kg liposomal amphotericin and ABLC, there was a nonsignificant trend toward a higher frequency of hypokalemia among patients receiving ABLC (37.2%) than among those receiving the 3-mg/kg dose of liposomal amphotericin (22.4%; $p=0.041$). The authors also claim a nonsignificant trend toward a higher frequency of anemia among patients receiving ABLC (59.0%) than among those receiving either the 3-mg/kg dose of liposomal amphotericin (36.5%) although the documented p value was $p=0.004$. [Note: Our recalculation also suggests a $p < 0.01$] Both liposomal amphotericin groups (3-mg/kg/d and 5-mg/kg/d) had lower rates of toxicity-related discontinuations of therapy than ABLC (12.9% and 12.3% vs. 32.1%; $P=0.004$).

2. How precise was the estimate of the treatment effect?

No 95% confidence intervals were reported by the authors.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. While there are already published comparisons of toxicity between the conventional deoxycholate formulation and either amphotericin B colloidal dispersion (ABCD) or liposomal amphotericin B, there have been no published, randomized, blinded comparisons of the relative toxicity of ABLC and liposomal amphotericin B. Thus, this study is the first randomized, double-blind evaluation of the safety of two lipid formulations of amphotericin B showing that ABLC at a dose of 5mg/kg is more toxic than liposomal amphotericin at a dose of 3mg/kg (with the exception of overall IRAE after the first day of treatment) or 5mg/kg. The results of the study are consistent across categories of toxicity and encompass both infusion-related toxicity and renal toxicity.

2. Were all clinically important outcomes considered?

Yes.

3. Are the likely treatment benefits worth the potential harms and costs?

Depending on the type of fungal infection being treated, the recommended dose of liposomal amphotericin B may vary from 3-5mg/kg/day compared to 5mg/kg/day for ABLC. In Canada, the approximate daily cost of liposomal amphotericin B (Ambisone[®], Fujisawa) for a 70 kg patient at a dose of 3mg/kg and 5mg/kg is \$882 CAN and \$1,470 CAN, respectively. A 5mg/kg regimen of ABLC (Abelcet[®], The Liposome Company) for this patient would cost approximately \$800 CAN.

Commentary

Up until recently, liposomal amphotericin was much more expensive than ABLC and thus the obvious question arising from this trial is whether the reduced toxicity of liposomal amphotericin B is compelling enough to justify the extra dollars? However, recently Fujisawa has decreased the acquisition cost for liposomal amphotericin in Canada such that the difference between preparations is currently less than \$100 CAN/day for a 3mg/kg dose and \$500 CAN/day for a 5mg/kg dose in a 70 kg patient. While the apparently superior safety profile of liposomal amphotericin may justify the increased cost associated with it, one must also consider the available efficacy data when trying to determine which agent to use. Unfortunately these agents have been used to treat different invasive fungal infections, in different patient populations and with varying dosage regimens. In addition, all the comparative studies have been in small numbers of patients using historical controls or for empiric therapy. While this study does not provide conclusive data with respect to the efficacy of the various lipid formulations, it does provide compelling toxicity data.

To date, there have been studies comparing toxicity between amphotericin B and the lipid formulations; however, there have not been any head to head comparisons of the various lipid-based agents. Thus, this is the first well-designed study to look at infusion-related reactions and nephrotoxicity between two different amphotericin-lipid formulations. This study was designed to examine relative product toxicities and although the efficacy of the two formulations is a secondary endpoint, the trial does not have sufficient statistical power to detect a difference. Laying aside the issue of efficacy, the results of the study show that liposomal amphotericin had a lower incidence of chills/rigors as well as overall frequency of infusion-related reactions on day 1 (when no premedications were allowed) as well as after the first day (when premedications were allowed) compared to ABLC. However, with premedications, the differences between liposomal amphotericin and ABLC were substantially lower.

The adverse event of greater concern with amphotericin is nephrotoxicity. These investigators found that the incidence of nephrotoxicity was higher for the ABLC group than the liposomal amphotericin treated neutropenic patients in the dosage regimens employed. In a different study conducted by the same investigators, increases in serum creatinine to >2.5mg/dL with the use of amphotericin led to hemodialysis and was associated with greater mortality. This trial clearly showed a larger percentage of patients reached serum creatinine levels >2.5mg/dL with ABLC than liposomal amphotericin B. (1)

Reference

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Reviewer's profession/specialty: Infectious Diseases

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No 95% confidence intervals were reported by the authors.

Will the Results Help Me in Caring for My Patients?

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Yes. While there are already published comparisons of toxicity between the conventional deoxycholate formulation and either amphotericin B colloidal dispersion (ABCD) or liposomal amphotericin B, there have been no published, randomized, blinded comparisons of the relative toxicity of ABLC and liposomal amphotericin B. Thus, this study is the first randomized, double-blind evaluation of the safety of two lipid formulations of amphotericin B showing that ABLC at a dose of 5mg/kg is more toxic than liposomal amphotericin at a dose of 3mg/kg (with the exception

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of overall IRAE after the first day of treatment) or 5mg/kg. The results of the study are consistent across categories of toxicity and encompass both infusion-related toxicity and renal toxicity.

2. Were all clinically important outcomes considered?

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Commentary

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The adverse event of greater concern with amphotericin is nephrotoxicity. These investigators found that the incidence of nephrotoxicity was higher for the ABLC group than the liposomal amphotericin treated neutropenic patients in the dosage regimens employed. In a different study conducted by the same investigators, increases in serum creatinine to >2.5mg/dL with the use of amphotericin led to hemodialysis and was associated with greater mortality. This trial clearly showed a larger percentage of patients reached serum creatinine levels >2.5mg/dL with ABLC than liposomal amphotericin B. (1)

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;4:218-220.

The risk of hemorrhagic stroke after phenylpropanolamine ingestion: Just how strong is the data?

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Original Citation

Kernan WN, Viscoli CM, Brass LM, Broderick JP, Brott T, Feldmann E, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med* 2000;343:1826-32. [PubMed Cit](#)

Overall Study Question

Over the past 20 years, more than 30 case reports have suggested a causal relationship between phenylpropanolamine (PPA), a common ingredient in over-the-counter appetite suppressants and cold remedies, and hemorrhagic stroke. To characterize this relationship, a multi-center, nested case-controlled study was conducted. The three objectives of the study were to 1) estimate the association between hemorrhagic stroke and the use of appetite suppressants containing PPA and any first use of products containing PPA among women, 2) estimate the association between hemorrhagic stroke and the use of any product containing PPA among both men and women, and 3) to estimate the association between hemorrhagic stroke and type of PPA and type of PPA exposure among both men and women.

Are the Results of the Study Valid?

1. Were there clearly identified comparison groups that were similar with respect to important determinants of outcome, other than the one of interest?

No. Patients with symptomatic subarachnoid hemorrhage or intracranial hemorrhage were identified and matched with two controls for each subject according to age, sex, and race through random digit dialing.

Baseline demographics, however, were significantly different between subjects and controls. Compared to controls, study subjects were more likely to be black, have a lower level of education, smoke, have hypertension, have a family history of hemorrhagic stroke, report regular alcohol use, and report cocaine use the day of or before the stroke. Study patients were also more likely to have used agents containing caffeine or nicotine and less likely to have used nonsteroidal anti-inflammatory drugs in the period three days prior to the stroke. To compensate for this, the investigators adjusted for all measured and significant potential confounders that, when added to the conditional logistic model, resulted in at least a ten percent variability in the matched odds ratio. The only variables that met these criteria were race, history of hypertension, and smoking status. The rest of the potential confounders were deemed to be insignificant.

2. Were the exposures and outcomes measured in the same way in the groups being compared?

Yes. For each patient the focal time or index day was defined as the calendar day that marked the onset of symptoms. Patients were then categorized according to PPA use. The window of exposure was defined as 72 hours preceding the index day. Patients who had used PPA-containing products less than 24 hours prior to the index day, but not during the 14 days prior, were labeled "first users" and were included in a sub-analysis.

Yes. For each patient the focal time or index day was defined as the calendar day that marked the onset of symptoms. Patients were then categorized according to PPA use. The window of exposure was defined as 72 hours preceding the index day. Exposure to PPA was ascertained through direct patient interview with a structured questionnaire when possible, or by telephone interview if a meeting could not be arranged within 30 days of the index day. During the interview, patients were asked to produce all medications taken two weeks prior to the index day, or identify them from a book containing photographs of packages. The investigators claimed to limit the risk of recall bias by conducting a structured interview, blinding patients to the study hypothesis, and conducting phone interviews if meetings could not be arranged within 30 days. The ratio of patients interviewed in person to those who were interviewed by phone was not stated. Patients who had used PPA-containing products less than 24 hours prior to the index day, but not during the 14 days prior, were labeled "first users" and were included in a sub-analysis.

3. Was the follow-up sufficiently long and complete?

Yes. Since patients were identified retrospectively (i.e., after a stroke had occurred), long-term follow up was unnecessary. However, control subjects were identified within 30 days of the patient's stroke to account for potential seasonal differences in PPA exposure.

4. Is the temporal relationship correct?

Yes.

5. Is there a dose-response gradient?

Potentially. The median dose of PPA in current male and female users from the control group was 75 mg. In a supplementary analysis, the investigators calculated point estimates of the odds ratio for those patients using less than or greater than a 75 mg dose. The odds ratio for the higher dose approached significance (2.30, 95% CI 0.96-5.54, $p=0.06$), indicating that there may be a dose effect, however this cohort analysis did not have adequate power to detect such a difference.

What were the Results?

1. How strong is the association between exposure and outcome?

Twenty-seven of 702 (3.8%) hemorrhagic stroke patients and 33 (2.4%) of 1376 control subjects had used PPA less than three days before the index event. The investigators found that women having a hemorrhagic stroke were more likely to have used PPA-containing products in the prior three days than the control group, yielding an odds ratio (OR) of 1.98 (95% CI, 1.00-3.90, $p=0.05$). Furthermore, women having a hemorrhagic stroke were more likely to have used PPA-containing appetite suppressants than the control group (OR=16.58, 95% CI 1.51-182.21, $p=0.02$). This finding remained significant when both men and women were included in the analysis despite the fact that no males used PPA-containing appetite suppressants (OR=15.92; 95% CI, 1.38-184.13, $p=0.03$). No significant difference was found among males who used PPA products.

2. How precise is the estimate of risk?

The use of conditional logistic models for the statistical analysis of this study was appropriate, as this procedure permits the investigator to control for potential confounding differences between the two groups. The difference between the two groups at baseline, however, raises questions about the internal validity of this study. Although the authors claim to have controlled for any measured and significant confounder that varied the results by more than 10%, this study may have involved a sample size that was too small to accurately identify significant confounders assuming that no variables were overlooked during the data collection. Only a prospective, randomized, clinical trial with comparable groups of subjects can confirm such an association. Such a trial is unlikely to be conducted because of ethical considerations.

Will the Results Help Me in Caring for My Patients?

1. Are the results applicable to my practice?

Yes. This study suggests that the use of PPA, especially as an appetite suppressant, may increase the risk of hemorrhagic stroke in female patients. It is unclear whether there is an increased risk

among males who use PPA in cough and cold products or appetite suppressants as only six of 319 male patients and 13 of 626 male controls used PPA three days prior to the index event.

2. What is the magnitude of the risk?

The results of this study suggest that one of every 107,000 to 3,268,000 women will experience a hemorrhagic stroke, should they use appetite suppressants containing PPA. Although this risk may seem small, the U.S. Food and Drug Administration claim that in 1999, six billion doses of medicines containing PPA were sold in this country alone. This would suggest that a significant number of people could be at risk for this serious adverse event.

3. Should I attempt to stop the exposure?

As a result of this study, PPA-containing products will no longer be available for sale in Canada or the United States. Whether this rapid response is warranted is debatable. Ideally, a prospective, placebo-controlled trial with better matched subjects and controls would be able to confirm or disprove the results of this study. Regardless, the FDA has answered this question for us.

Commentary

While this study demonstrated an apparent increased risk of hemorrhagic stroke among women who use PPA-containing products (primarily appetite suppressants) it was not powered to detect a difference among men. Despite attempts to control for baseline differences between groups in the statistical analysis, there were significant differences between the experimental and control groups. At this time it may be prudent to avoid PPA-containing products for both men and women but further investigation is warranted into risk factor identification and differentiating risk according to frequency and type of use (i.e., daily use of appetite suppressants versus short term use of cold remedies). The information from this study would be more useful if the mechanism behind the increased risk of stroke was understood, and if differences in risk between men and women could be better elucidated. However, considering that the incidence of PPA use among stroke patients appears to be very low, it is unlikely that a study with adequate power would be feasible. Further in vitro study and perhaps animal model studies need to be done to identify the mechanism for this serious adverse event.

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The Journal of Informed Pharmacotherapy

The risk of hemorrhagic stroke after phenylpropanolamine ingestion: Just how strong is the data?

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Reviewer's profession/specialty: Critical Care

Original Citation

Kernan WN, Viscoli CM, Brass LM, Broderick JP, Brott T, Feldmann E, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med* 2000;343:1826-32.

Overall Study Question

Over the past 20 years, more than 30 case reports have suggested a causal relationship between phenylpropanolamine (PPA), a common ingredient in over-the-counter appetite suppressants and cold remedies, and hemorrhagic stroke. To characterize this relationship, a multi-center, nested case-controlled study was conducted. The three objectives of the study were to 1) estimate the association between hemorrhagic stroke and the use of appetite suppressants containing PPA and any first use of products containing PPA among women, 2) estimate the association between hemorrhagic stroke and the use of any product containing PPA among both men and women, and 3) to estimate the association between hemorrhagic stroke and type of PPA and type of PPA exposure among both men and women.

Are the Results of the Study Valid?

1. Were there clearly identified comparison groups that were similar with respect to important determinants

of outcome, other than the one of interest?

No. Patients with symptomatic subarachnoid hemorrhage or intracranial hemorrhage were identified and matched with two controls for each subject according to age, sex, and race through random digit dialing.

Baseline demographics, however, were significantly different between subjects and controls. Compared to controls, study subjects were more likely to be black, have a lower level of education, smoke, have hypertension, have a family history of hemorrhagic stroke, report regular alcohol use, and report cocaine use the day of or before the stroke. Study patients were also more likely to have used agents containing caffeine or nicotine and less likely to have used nonsteroidal anti-inflammatory drugs in the period three days prior to the stroke. To compensate for this, the investigators adjusted for all measured and significant potential confounders that, when added to the conditional logistic model, resulted in at least a ten percent variability in the matched odds ratio. The only variables that met these criteria were race, history of hypertension, and smoking status. The rest of the potential confounders were deemed to be insignificant.

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2. Were the exposures and outcomes measured in the same way in the groups being compared?

Yes. For each patient the focal time or index day was defined as the calendar day that marked the onset of symptoms. Patients were then categorized according to PPA use. The window of exposure was defined as 72 hours preceding the index day. Patients who had used PPA-containing products less than 24 hours prior to the index day, but not during the 14 days prior, were labeled "first users" and were included in a sub-analysis.

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3. Was the follow-up sufficiently long and complete?

Yes. Since patients were identified retrospectively (i.e., after a stroke had occurred), long-term follow up was unnecessary. However, control subjects were identified within 30 days of the patient's stroke to

account for potential seasonal differences in PPA exposure.

4. Is the temporal relationship correct?

Yes.

5. Is there a dose-response gradient?

Potentially. The median dose of PPA in current male and female users from the control group was 75 mg. In a supplementary analysis, the investigators calculated point estimates of the odds ratio for those patients using less than or greater than a 75 mg dose. The odds ratio for the higher dose approached significance (2.30, 95% CI 0.96-5.54, $p=0.06$), indicating that there may be a dose effect, however this cohort analysis did not have adequate power to detect such a difference.

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J Inform Pharmacother 2001;4:218-220.

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;4:221-223.

Is the dopamine agonist pramipexole an alternative to levodopa for treatment of early Parkinson disease?

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Reviewer's email address: demacleo@sehcc.health.nb.ca

Reviewer's profession/specialty: Resident/Family practice and Geriatrics

Original Citation

Anon. Pramipexole vs. levodopa as initial treatment for Parkinson disease: a randomized controlled trial. *JAMA* 2000;284:1931-1938. [PubMed Cit](#)

Overall Study Question

The objective of this study was to compare the development of dopaminergic motor complications after initial treatment of Parkinson disease (PD) with pramipexole versus levodopa. Patients with early PD who required dopaminergic therapy were enrolled between October 1996 and August 1997. Primary outcome was the time to first occurrence of any of three dopaminergic complications: wearing off, dyskinesias or on-off motor fluctuations. Secondary outcomes included: changes in scores on UPDRS (Unified Parkinson's disease rating scale), PDQUALIF (Parkinson's disease quality of life scale) and EuroQol assessed from baseline to study completion. A substudy to evaluate the potential neuroprotective effect of pramipexole on dopamine neurons was also performed. This was done by measuring decline in beta-CIT uptake using single photon emission computed tomography (SPECT). beta-CIT uptake is a marker of dopamine transporter density in dopaminergic neuron terminals in the striatum. Postmortem data have shown reduced dopaminergic transporter density in PD patients.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Eligible patients were randomized 1:1 to either pramipexole or carbidopa/levodopa. Randomization was stratified by investigator and block.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. A flow chart was provided to graphically account for all those screened for study participation. The 301 patients enrolled were randomized to two groups: 151 received pramipexole (23 withdrew due to adverse effects) and 150 received levodopa (19 withdrew due to adverse effects). No patients were lost to follow-up. Data analysis was based on an intention-to-treat basis and involved all randomized patients.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. Both clinicians and patients were blinded to treatment assignment. This was accomplished using a double dummy technique.

4. Were the groups similar at the start of the trial?

Yes. The two treatment groups were similar at baseline with regard to demographic and clinical variables. All patients were in Hoehn and Yahr stages I, II or III, with similar divisions among these stages between the two treatment groups. Hoehn and Yahr staging is a measure of PD severity typically used in clinical practice. The pre-study quality of life assessment scores (PDQUALIF, EuroQol) were also similar between the two groups, as was prior use of levodopa, selegiline, amantadine and anticholinergic drugs.

5. Aside from the experimental intervention, were the groups treated equally?

Yes. Patients in both groups received the same number of follow-up visits. For patients with residual disability, the dosage of either study drug was escalated during the first ten weeks, up to a maximum of 4.5mg pramipexole or 150/600mg carbidopa/levodopa. From week 11 to month 23.5, investigators were permitted to add open label regular release levodopa (sustained release preparations were not allowed) to treat continuing or emerging disability in either group.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

The primary outcome was the time to first occurrence of any of three dopaminergic complications: wearing off, dyskinesias and on-off motor fluctuations. Pramipexole

treatment resulted in 42/151 patients (28%) developing dopaminergic complications vs. 76/150 patients (51%) treated with levodopa [hazard ratio (HR)=0.45, $p<0.001$]. These results translate into an absolute risk reduction (ARR) of 22.9% and a number needed to treat (NNT) of 4-5 patients (95% confidence interval (CI) = 3-8 patients). Therefore, 4-5 patients would need to be treated over 23.5 months with pramipexole instead of levodopa to postpone the occurrence of a dopaminergic complication in one patient. Differences between the two treatment arms were also reported for some of the secondary outcomes. More patients in the pramipexole group (53%) versus the levodopa group (39%) required supplemental levodopa during the trial [HR=1.54 (1.09-2.17), $p=0.02$].

Mean improvement in the total UPDRS score from baseline to 23.5 months was greater in the levodopa group than in the pramipexole group 9.2 vs. 4.5 points ($p<0.001$). Quality of life scores improved in both groups initially and then declined over time, with the levodopa group having higher scores at the end of the study ($p=0.006$). Finally, somnolence was more common in pramipexole treated patients than in levodopa treated patients (32.4% vs. 17.3%, $p=0.003$). In the substudy, there was a greater mean decline in striatal beta-CIT uptake in the levodopa group (24.8%) compared with the pramipexole group (20%). This difference was not significant ($p=0.15$).

2. How precise was the estimate of the treatment effect?

Results associated with the primary endpoint included a HR of 0.45 with a 95% CI (0.30-0.66). The 95%CI for ARR and NNT can be calculated to further demonstrate the precision of the results: ARR (15.2-33.5%), NNT (3-7).

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. The well-defined inclusion/exclusion criteria would allow results to be applied to a definable population. However, the benefit in decreased dopaminergic complications demonstrated with pramipexole must be evaluated with consideration of the difference in efficacy, quality of life and adverse effects between levodopa and pramipexole.

2. Were all clinically important outcomes considered?

Most outcomes were considered including time to development of dopaminergic complications, efficacy, adverse effects and quality of life. Cost was not discussed.

3. Are the likely treatment benefits worth the potential harms and costs?

Although the time to development of dopaminergic complications was significantly greater in the pramipexole group, there were also significantly more patients who experienced somnolence, hallucinations and edema (generalized and peripheral). As well, it is important to consider the

difficulty that a patient with Parkinson disease may have in appreciating the benefit of delayed dopaminergic complications compared with the reality of the side effects and decreased quality of life (e.g. loss of a driver's license) that can be associated with the use of pramipexole.

Commentary

Although levodopa is the gold standard for treatment of Parkinson disease, there has been considerable concern about the potential long term risks. It is postulated that early exposure to levodopa in the course of Parkinson disease can lead to increased dopaminergic complications. This has led to a search for alternative treatments that can be used to delay the initiation of levodopa treatment. This study looks at the relationship between both levodopa and a dopamine agonist (pramipexole) to the development of dopaminergic complications and in a substudy, neuronal loss. The results do show a significant increase in time to onset of the dopaminergic complications with pramipexole; however, it is important to note that these dopaminergic complications still occurred with pramipexole. Although, not statistically significant, pramipexole did show a slower decline in beta-CIT striatal uptake. For those patients in whom the delay of initiation of levodopa is desirable, the use of pramipexole (a dopamine agonist) may be an alternative; however, the clinician must weigh the risks and benefits for each individual patient.

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J Inform Pharmacother 2001;4:221-223.

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Issues in Pharmacotherapy Practice

Hemorrhagic Transformation after Reperfusion Therapy for Acute Ischemic Stroke

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Abstract

Objective: To introduce the controversy in the classification of hemorrhagic transformation (HT) and to identify risk factors for poor outcome due to HT after reperfusion therapy for acute ischemic stroke.

Data Source: A MEDLINE search was performed (1995 – September, 2000) to identify relevant English-language publications, including clinical trials and review articles with the key words of *hemorrhagic transformation*, *tissue plasminogen activator*, *streptokinase* and *stroke*.

Study Selection and Data Extraction: Controlled clinical trials of reperfusion therapy in acute ischemic stroke patients were selected to identify the known risk factors for HT.

Data Synthesis and Results: There are two methods of classification of HT. One method is based upon purely radiological criteria, while the other relies on a combination of clinical symptoms and radiological findings. In three clinical trials that describe successful reperfusion strategies in human stroke patients, the following risk factors for the development of HT associated with poor outcome were identified: fibrinolysis, baseline CT changes consistent with ischemia, and severity of symptoms. The rates of symptomatic HT range from 5-10% in these trials. The relative risk (treatment event rate versus placebo event rate) varies based on the placebo rate, which is important to consider in assessing the safety of the therapeutic intervention.

Conclusion: HT can worsen the outcome of an ischemic stroke and is clearly associated with reperfusion strategies such as fibrinolytics and ancrod. Patients with large ischemic strokes, characterized by early CT findings of ischemia at baseline and poor clinical presentation, are at the highest risk of HT. However, these same patients are at high risk for a poor outcome regardless of the treatment they receive and may still benefit from reperfusion. Protocol violations with tPA use for acute ischemic stroke has been identified as an important contributor to the development of symptomatic HT. Each patient must be individually assessed for the relative risks and benefits of reperfusion therapy before being treated according to a carefully executed protocol.

J Inform Pharmacother 2001;4:300-305.

Introduction

Hemorrhagic transformation (HT) of an ischemic lesion is a common occurrence in stroke patients, occurring in up to 70% of patients in one published series. (1) In fact, it has only been with the advent of sensitive imaging techniques, performed at prescribed times after stroke onset, that the true incidence of HT is emerging. For the most part, HT is thought to be without clinical consequence, or asymptomatic, and some investigators have gone as far as to say that some HT may be a good

prognostic sign as it demonstrates that reperfusion has occurred and the tissue may return to normal function. (2)

Interest in HT has been heightened by the introduction of reperfusion strategies designed to dislodge the offending clot and reestablish cerebral blood flow. All of the reperfusion strategies proven effective in improving functional outcome after ischemic stroke have done so through a manipulation of the endogenous fibrinolytic system. (3-5) Because of this, all of them carry increased the risk of HT, which is sometimes fatal.

The purpose of this paper is to introduce the controversy in the classification of HT and to identify risk factors for poor outcome due to HT following reperfusion therapy.

Hemorrhagic Transformation after Acute Ischemic Stroke

HT describes a wide range of radiological phenomena. The European Cooperative Acute Stroke Study (ECASS) investigators (6), have classified HT into hemorrhagic infarction (HI) and parenchymal hematoma (PH). HI1 represents petechial (spotty) hemorrhages in the infarcted area while HI2 represents confluent petechiae. In PH1, a clot is evident and the hemorrhage is confined to <33% of the area of the infarct and in PH2 the hemorrhage is larger, is usually associated with mass effect, and can be in an area distal to the ischemic lesion. It is generally accepted that PH2, especially when extended to the ventricles, is associated with a high early mortality rate. (6,7)

There are two main schools of thought regarding the classification of HT after ischemic stroke. The first is that only the radiological characteristics should be used to describe the main types of HT. This is the method used by the ECASS investigators and is based on the observation that HT often occurs in patients who deteriorate due to cerebral edema or other phenomena. (6,8-10) Using pure radiological criteria, the ECASS investigators were able to demonstrate that only PH2 (not HI1, HI2 or even PH1) significantly increased the risk of early deterioration and death (6).

The second approach to HT classification embraces the concept that the radiological characteristics of this phenomenon cannot be interpreted without considering the clinical course of the patient. In this strategy, HT is considered to be either symptomatic or asymptomatic. This second strategy has been popularized by the National Institute of Neurological Disorders and Stroke (NINDS) tPA Stroke Study Group. (3,11) It recognizes that small hemorrhages in crucial areas of the brain can be devastating and assumes that clinicians are the most qualified to assess whether an HT is "significant" or not.

Methods

MEDLINE searches (1995 – September 2000) were conducted to identify randomized clinical trials and subgroup analyses of hemorrhagic transformation after reperfusion therapy in ischemic stroke patients. The following key words were used: *hemorrhagic transformation*, *tissue plasminogen activator*, *streptokinase* and *stroke*.

Results

Streptokinase

Three hallmark randomized clinical trials using streptokinase for the treatment of acute ischemic stroke were identified. Although discontinued early due to excess deaths in the treatment groups, the streptokinase studies contributed important information regarding the patients at risk of symptomatic intracerebral hemorrhage after reperfusion therapy. (7,12-14) All three studies included in Table 1 identified streptokinase as an important contributor to HT. Other contributors to HT are also included in the table. For example, the use of early ASA after thrombolytic treatment, as seen in the Multicentre Acute Stroke Trial – Italy (MAST-I), significantly increased the risk of symptomatic intracerebral hemorrhage (ICH). (7) These studies support the strict prohibition of antithrombotic treatment for the first 24 hours after fibrinolysis. However, whether the agent (streptokinase), the

time of administration (4-6 hours from onset of symptoms) or the dose of streptokinase (1.5 million units) is the most important factor contributing to the high mortality from ICH in these studies remains unclear.

Table 1. Streptokinase Hemorrhagic Transformation

Study (Ref)	Treatment Window	Risk Factors	Placebo Rates	Treatment Rates
MAST-I (7,12)	6 hours	SK SK + ASA	Symptomatic=0.6%	SK=6% SK+ASA=10%
MAST-E (13)	6 hours	SK Baseline CT changes Diabetes SK with decreased LOC	Symptomatic=2.5% All= 31%	Symptomatic=21% All=62%
ASK (14)	4 hours	SK Time >3 hours	Symptomatic=2.4%	Symptomatic=13%

MAST-I=Multicenter Acute Stroke Trial - Italy; SK=Streptokinase; ASA=aspirin; MAST-E=Multicenter Acute Stroke Trial - Europe; CT=computed tomography; LOC=level of consciousness; ASK=Australian Streptokinase Trial

Successful Reperfusion Strategies

In the three clinical trials in which reperfusion of the ischemic brain was shown to be effective in reducing disability at 90 days (4-6), the incidence of symptomatic HT ranged from 5-10% (2.5- to 10-fold the placebo rate for this event) and the definitions varied with each study. In a multivariable analysis of the NINDS study, only severity of stroke and CT changes at baseline were shown to be important predictors of symptomatic HT. (4,9,10) Increased age was associated with symptomatic HT (9), but much of the increased risk was accounted for by an increased severity of stroke in these patients. (4)

Table 2. Successful Reperfusion Strategies - Hemorrhagic Transformation

Study (Ref)	Treatment Window	Risk Factors	Placebo Rates	Treatment Rates
NINDS (4)	3 hours	Severity Edema or mass effect on CT TPA	Symptomatic=0.6% Asymptomatic=2.6%	Symptomatic=6.4% Asymptomatic=4.2%
PROACT II (5)	6 hours	Severity (CT exclusion criteria)	Symptomatic=2% All=13%	Symptomatic=10% All=35%
STAT (6)	3 hours	Fibrinogen level at 9-72 hours	Symptomatic=2% Asymptomatic=10.7%	Symptomatic=10% Asymptomatic=20.3%

ECASS=European Cooperative Acute Stroke Study; HI=hemorrhagic infarction; PH=parenchymal hematoma; CT=computed tomography; TPA=tissue plasminogen activator; NINDS=National Institute of

Neurologic Disorders and Stroke tPA Stroke Trial; PROACT=Prolyse in Acute Cerebral Thromboembolism; STAT=Stroke Treatment with Ancrod Trial

Unsuccessful tPA Trials

Attempts to widen the therapeutic window beyond three hours for intravenous tPA in acute ischemic stroke have not been successful. ECASS I and II, along with Atlantis and A0276g all involved the use of tPA after 3 hours. (15-18) ECASS I and II and A0276g each had 6 hour time windows, while Atlantis had a 3-5 hour window. The symptomatic HT rates in tPA-treated patients were 7% in Atlantis and 8.8% in ECASS II, just slightly higher than the 6.4% rate seen in NINDS. (16,17) However, the A0276g trial reported an 11% symptomatic HT rate, which was substantially influenced by a rate of 18.2% in the patients treated five to six hours after symptom onset. A direct influence of time of treatment on the incidence of HT was confounded by a nine-fold increase in the number of severe strokes (NIHSS > 20) in the patients who received tPA between 5 and 6 hours after onset. (18)

Table 3. Unsuccessful tPA Trials - Hemorrhagic Transformation

Study (Ref)	Treatment Window	Risk Factors	Placebo Rates	Treatment Rates
ECASS I (9,15)	6 hours	Severity (HI) Baseline CT changes (HI) Increased age (PH) TPA (PH)	HI=31% PH=7%	HI=22% PH=21%
ECASS II (10,16)	6 hours	TPA	Symptomatic=3.4% PH=3.1%	Symptomatic=8.8% PH=12.4%
ATLANTIS (17)	3-5 hours	TPA	Symptomatic=1.1% Asymptomatic=4.7%	Symptomatic=7% Asymptomatic=11.4%
A0276g (18)	6 hours	TPA Time to treatment > 5 hours	Symptomatic=0%	Symptomatic=11%

ECASS=European Cooperative Acute Stroke Study; TPA=tissue plasminogen activator; HI=hemorrhagic infarction; PH=parenchymal hematoma

Postmarketing Experience with tPA

Since the first evidence of tPA safety and efficacy in treating patients with acute ischemic stroke, various groups have published their experiences with using the therapy in clinical practice. In 5 independent case series involving from 30 to 389 patients per series, the rates of symptomatic HT ranged from 3-7%. This was consistent with event rates reported in the NINDS trial and reflective of acceptable risk. (19-23) However, in a report describing the experience of several hospitals from Cleveland, Ohio, investigators reported an alarming symptomatic HT rate of 15%, accompanied by a relatively high 15% in-hospital mortality rate. (23) Of note, the investigators also reported a 50% incidence of protocol violations, the most common of which was an inappropriate use of antithrombotic agents during the first 24-hour period following tPA administration.

A consistent theme in all of the published reports of tPA for stroke in clinical practice is the importance of utilizing a strict protocol, based on the NINDS tPA Stroke trial. Deviation from the

protocol can have disastrous results in terms of symptomatic HT and early mortality.

Discussion

HT can be a devastating consequence of thrombolytic therapy in patients with acute ischemic stroke. Using radiological criteria alone to categorize HT as either parenchymal hematoma or hemorrhagic infarction has a high degree of objectivity and inter-rater reliability and appears to enable a prediction of early deterioration and mortality. Most experts agree; however, that a combination of clinical and radiological criteria must be used to adequately judge the significance of HT to an individual patient. For this reason, most clinical trials have enumerated HT as being either symptomatic or asymptomatic and clinical practice has followed this lead.

The patients at highest risk of symptomatic HT are those individuals who present with a severe stroke (i.e. a National Institute of Health Stroke Scale (NIHSS) greater than 20) (4) and those with early evidence of edema and mass effect on the initial CT. (4,9,10) These parameters are probably markers for the patients with the most severe damage to the microvasculature. Del Zoppo maintains that damage to the endothelium and basal lamina of the cerebral vasculature is necessary for the leakage of blood into the brain. (24) Symptomatic HT rates of up to 30% were observed in the highest risk patients. This includes patients who receive tPA outside of a carefully executed protocol. An alarmingly high incidence of protocol violations (50%), the most common being antithrombotic treatment within 24 hours of receiving tPA, was reported by Cleveland investigators. (23)

Although no randomized clinical trial evidence exists, another factor thought to be important in reducing the risk of HT after reperfusion in stroke patients is management of elevated blood pressure. Experimental stroke studies have demonstrated a direct correlation between blood pressure and risk of HT (25) and treatment of blood pressure elevation has been shown to decrease HT size. (26) Guidelines for the management of blood pressure elevation in patients who have received tPA have been published and should be followed. (27)

Patients at high risk of symptomatic HT after tPA therapy for stroke are also at high risk of a poor outcome without HT. (11) In fact, despite their increased risk of HT, the NINDS investigators reported an increased likelihood of a good outcome (albeit small) when patients with severe stroke received tPA. (11) It is clear that each ischemic stroke patient must be evaluated individually for the relative risks and benefits of reperfusion therapy.

Conclusion

HT can worsen the outcome of an ischemic stroke and is clearly associated with reperfusion strategies such as fibrinolytics and ancrod. Patients with large ischemic strokes, characterized by early CT findings of ischemia at baseline and poor clinical presentation, are at the highest risk of HT. However, these same patients are at high risk for a poor outcome regardless of the treatment they receive and may still benefit from reperfusion. Protocol violations with tPA use for acute ischemic stroke has been identified as an important contributor to the development of symptomatic HT. Each patient must be individually assessed for the relative risks and benefits of reperfusion therapy before being treated according to a carefully executed protocol.

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Hemorrhagic Transformation after Reperfusion Therapy for Acute Ischemic Stroke

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Objective: To introduce the controversy in the classification of hemorrhagic transformation (HT) and to identify risk factors for poor outcome due to HT after reperfusion therapy for acute ischemic stroke.

Data Source: A MEDLINE search was performed (1995 – September, 2000) to identify relevant English-language publications, including clinical trials and review articles with the key words of *hemorrhagic transformation, tissue plasminogen activator, streptokinase and stroke*.

Study Selection and Data Extraction: Controlled clinical trials of reperfusion therapy in acute ischemic stroke patients were selected to identify the known risk factors for HT.

Data Synthesis and Results: There are two methods of classification of HT. One method is based upon purely radiological criteria, while the other relies on a combination of clinical symptoms and radiological findings. In three clinical trials that describe successful reperfusion strategies in human stroke patients, the following risk factors for the development of HT associated with poor outcome were identified: fibrinolysis, baseline CT changes consistent with ischemia, and severity of symptoms. The rates of symptomatic HT range from 5-10% in these trials. The relative risk (treatment event rate versus placebo event rate) varies based on the placebo rate, which is important to consider in assessing the safety of the therapeutic intervention.

Conclusion: HT can worsen the outcome of an ischemic stroke and is clearly associated with reperfusion strategies such as fibrinolytics and anecord. Patients with large ischemic strokes, characterized by early CT findings of ischemia at baseline and poor clinical presentation, are at the highest risk of HT.

However, these same patients are at high risk for a poor outcome regardless of the treatment they receive and may still benefit from reperfusion. Protocol violations with tPA use for acute ischemic stroke has been identified as an important contributor to the development of symptomatic HT. Each patient must be individually assessed for the relative risks and benefits of reperfusion therapy before being treated according to a carefully executed protocol.

J Inform Pharmacother 2001;4:300-305.

Hemorrhagic transformation (HT) of an ischemic lesion is a common occurrence in stroke patients, occurring in up to 70% of patients in one published series. (1) In fact, it has only been with the advent of sensitive imaging techniques, performed at prescribed times after stroke onset, that the true incidence of HT is emerging. For the most part, HT is thought to be without clinical consequence, or asymptomatic, and some investigators have gone as far as to say that some HT may be a good prognostic sign as it demonstrates that reperfusion has occurred and the tissue may return to normal function. (2)

Interest in HT has been heightened by the introduction of reperfusion strategies designed to dislodge the offending clot and reestablish cerebral blood flow. All of the reperfusion strategies proven effective in improving functional outcome after ischemic stroke have done so through a manipulation of the endogenous fibrinolytic system. (3-5) Because of this, all of them carry increased the risk of HT, which is sometimes fatal.

The purpose of this paper is to introduce the controversy in the classification of HT and to identify risk factors for poor outcome due to HT following reperfusion therapy.

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Hemorrhagic Transformation after Acute Ischemic Stroke

HT describes a wide range of radiological phenomena. The European Cooperative Acute Stroke Study (ECASS) investigators (6), have classified HT into hemorrhagic infarction (HI) and parenchymal hematoma (PH). HI1 represents petechial (spotty) hemorrhages in the infarcted area while HI2 represents confluent petechiae. In PH1, a clot is evident and the hemorrhage is confined to <33% of the area of the infarct and in PH2 the hemorrhage is larger, is usually associated with mass effect, and can be in an area distal to the ischemic lesion. It is generally accepted that PH2, especially when extended to the ventricles, is associated with a high early mortality rate. (6,7)

There are two main schools of thought regarding the classification of HT after ischemic stroke. The first is that only the radiological characteristics should be used to describe the main types of HT. This is the method used by the ECASS investigators and is based on the observation that HT often occurs in patients who deteriorate due to cerebral edema or other phenomena. (6,8-10) Using pure radiological criteria, the ECASS investigators were able to demonstrate that only PH2 (not HI1, HI2 or even PH1) significantly increased the risk of early deterioration and death (6).

The second approach to HT classification embraces the concept that the radiological characteristics of this phenomenon cannot be interpreted without considering the clinical course of the patient. In this strategy, HT is considered to be either symptomatic or asymptomatic. This second strategy has been popularized by the National Institute of Neurological Disorders and Stroke (NINDS) tPA Stroke Study Group. (3,11) It recognizes that small hemorrhages in crucial areas of the brain can be devastating and assumes that clinicians are the most qualified to assess whether an HT is "significant" or not.

Methods

MEDLINE searches (1995 – September 2000) were conducted to identify randomized clinical trials and subgroup analyses of hemorrhagic transformation

after reperfusion therapy in ischemic stroke patients. The following key words were used: *hemorrhagic transformation, tissue plasminogen activator, streptokinase* and *stroke*.

Results

Streptokinase

Three hallmark randomized clinical trials using streptokinase for the treatment of acute ischemic stroke were identified. Although discontinued early due to excess deaths in the treatment groups, the streptokinase studies contributed important information regarding the patients at risk of symptomatic intracerebral hemorrhage after reperfusion therapy. (7,12-14) All three studies included in Table 1 identified streptokinase as an important contributor to HT. Other contributors to HT are also included in the table. For example, the use of early ASA after thrombolytic treatment, as seen in the Multicentre Acute Stroke Trial – Italy (MAST-I), significantly increased the risk of symptomatic intracerebral hemorrhage (ICH). (7) These studies support the strict prohibition of antithrombotic treatment for the first 24 hours after fibrinolysis. However, whether the agent (streptokinase), the time of administration (4-6 hours from onset of symptoms) or the dose of streptokinase (1.5 million units) is the most important factor contributing to the high mortality from ICH in these studies remains unclear.

Successful Reperfusion Strategies

In the three clinical trials in which reperfusion of the ischemic brain was shown to be effective in reducing disability at 90 days (4-6), the incidence of symptomatic HT ranged from 5-10% (2.5- to 10-fold the placebo rate for this event) and the definitions varied with each study. In a multivariable analysis of the NINDS study, only severity of stroke and CT changes at baseline were shown to be important predictors of symptomatic HT. (4,9,10)

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Table 1. Streptokinase Hemorrhagic Transformation

Study (Ref)	Treatment Window	Risk Factors	Placebo Rates	Treatment Rates
MAST-I (7,12)	6 hours	SK SK + ASA	Symptomatic=0.6%	SK=6% SK+ASA=10%
MAST-E (13)	6 hours	SK Baseline CT changes Diabetes SK with decreased LOC	Symptomatic=2.5% All= 31%	Symptomatic=21% All=62%
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MAST-I=Multicenter Acute Stroke Trial - Italy; SK=Streptokinase; ASA=aspirin; MAST-E=Multicenter Acute Stroke Trial - Europe; CT=computed tomography; LOC=level of consciousness; ASK=Australian Streptokinase Trial

Table 2. Successful Reperfusion Strategies - Hemorrhagic Transformation

Study (Ref)	Treatment Window	Risk Factors	Placebo Rates	Treatment Rates
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ECASS=European Cooperative Acute Stroke Study; HI=hemorrhagic infarction; PH=parenchymal hematoma; CT=computed tomography; TPA=tissue plasminogen activator; NINDS=National Institute of Neurologic Disorders and Stroke tPA Stroke Trial; PROACT=Prolyse in Acute Cerebral Thromboembolism; STAT=Stroke Treatment with Ancrod Trial

Unsuccessful tPA Trials

Attempts to widen the therapeutic window beyond three hours for intravenous tPA in acute ischemic stroke have not been successful. ECASS I and II, along with Atlantis and A0276g all involved the use of tPA after 3 hours. (15-18) ECASS I and II and A0276g each had 6 hour time windows, while Atlantis had a 3-5 hour window. The symptomatic HT rates in tPA-treated patients were 7% in Atlantis and 8.8% in ECASS II, just slightly higher than the 6.4% rate seen in

NINDS. (16,17) However, the A0276g trial reported an 11% symptomatic HT rate, which was substantially influenced by a rate of 18.2% in the patients treated five to six hours after symptom onset. A direct influence of time of treatment on the incidence of HT was confounded by a nine-fold increase in the number of severe strokes (NIHSS > 20) in the patients who received tPA between 5 and 6 hours after onset. (18)

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Table 3. Unsuccessful tPA Trials - Hemorrhagic Transformation

Study (Ref)	Treatment Window	Risk Factors	Placebo Rates	Treatment Rates
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A consistent theme in all of the published reports of tPA for stroke in clinical practice is the importance of utilizing a strict protocol, based on the NINDS tPA Stroke trial. Deviation from the protocol can have disastrous results in terms of symptomatic HT and early mortality.

Discussion

HT can be a devastating consequence of thrombolytic therapy in patients with acute ischemic stroke. Using radiological criteria alone to categorize HT as either parenchymal hematoma or hemorrhagic infarction has a high degree of objectivity and inter-rater reliability and appears to enable a prediction of early deterioration and mortality. Most experts agree; however, that a combination of clinical and radiological criteria must be used to adequately judge the significance of HT to an individual patient. For this reason, most clinical trials have enumerated HT as being either symptomatic or asymptomatic and clinical practice has followed this lead.

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includes patients who receive tPA outside of a carefully executed protocol. An alarmingly high incidence of protocol violations (50%), the most common being antithrombotic treatment within 24 hours of receiving tPA, was reported by Cleveland investigators. (23)

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Issues in Pharmacotherapy Practice

Issues in Human Immunodeficiency Virus (HIV) Pharmacotherapy Practice: The Emerging Role of Pharmacotherapy Specialists in Enhancing Antiretroviral Success

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Abstract

Human immunodeficiency virus (HIV) pharmacotherapy has evolved into a highly complex clinical specialty requiring a delicate balance of art and science to achieve and maintain the therapeutic goals of complete viral suppression while maintaining quality of life. The complexity of the inter-relationship between the virology, pharmacology, pharmacokinetics, pharmacodynamics and patient-related factors creates a sizeable therapeutic challenge. Adherence to prescribed antiretrovirals remains the ultimate challenge as it has been shown that near perfect adherence is required to achieve adequate and sustained viral suppression. Innovative changes in clinical practice models have been proposed and implemented in an attempt to incorporate multiple disciplines for optimal patient management. The role of HIV pharmacotherapy specialists is evolving and may be paramount to successful antiretroviral management in this specialty arena. A review of the challenges of achieving virologic suppression clearly illustrates the value, and perhaps necessity, of incorporating HIV pharmacotherapists into the standard care of patients with HIV infection.

J Inform Pharmacother 2001;4:306-316.

Introduction

Significant advances in HIV pharmacotherapy include the enhanced understanding of viral replication in the human host, the ability to quantify viral load and correlate with clinical outcomes, the availability of tools to assess viral susceptibility, the development of new antiretroviral agents and a heightened appreciation of the importance of patient adherence to prescribed antiretroviral regimens to ensure successful virologic suppression (1). Despite advances and the availability of several sets of state-of-the-art treatment guidelines, no overall consensus has emerged with respect to when to initiate therapy and which agents to use to maximize virologic suppression (1-3). Most authorities would agree; however, that left untreated, viral replication causes life-threatening destruction of the immune system and the development of more genetically diverse and increasingly virulent strains, due to this highly mutable virus. Thus, complex antiretroviral regimens are necessary in most patients infected with HIV. Although many regimens appear effective, the optimal regimen or protocol to employ when initiating antiretroviral therapy remains unclear.

The goal of this paper is to describe the current standards of HIV care and the complexities and challenges that exist in effectively implementing these standards. The emerging role of HIV pharmacotherapy specialists (pharmacists specializing in clinical HIV care) in enhancing antiretroviral success will be discussed.

Disparity Between Efficacy and Effectiveness

Initiation of potent antiretroviral therapy has improved virologic and clinical outcomes of patients with HIV infection, such as decreasing incidence of opportunistic infections, hospitalizations and mortality (4,5). In vivo studies have provided data regarding the efficacy of new agents and new therapeutic combinations of antiretrovirals. In clinical trials, various combinations of protease inhibitors, nucleoside analogues and/or non-nucleoside reverse transcriptase inhibitors have reduced plasma HIV-1 RNA levels to less than 500 copies/mL in 60% to 90% of antiretroviral-naïve patients (6-11).

Of concern; however, is that the true effectiveness of these drugs (i.e. their benefits in routine clinical use) has been less than expected based on the results of the original clinical trials. In an urban HIV clinic, Lucas et al. found that less than 43% of previously antiretroviral-naïve patients who initiated therapy with one of these agents had an undetectable viral load at 3 months, 48.8% were undetectable at 3-7 months and only 38.4% were undetectable at 7-14 months (12). This falls far short of the therapeutic goal of 100% viral suppression and the 60-90% undetectable viral load rates reported in earlier clinical trials.

It would appear that once out of the rigors of participation in a clinical trial, with recruitment of only the most motivated, "ideal" patients, consistent counselling related to the study medications and regulated monitoring and follow-up, the effectiveness of antiretroviral agents is diminished. In clinical studies, there is typically a close evaluation of patients' lifestyles prior to recruitment to ensure that non-medical issues such as language barriers, childcare issues and employment barriers will not interfere with the study protocol. In addition, baseline physical exams aim to identify or rule out any pre-existing medical conditions that may be exacerbated by the introduction of the new medications or at least serve as a complete baseline to enable adequate assessment of any newly identified drug-related problems. Careful scrutiny of concomitant medication use minimizes the likelihood that drug interactions will interfere with the safety and/or efficacy of the new medications. Perhaps the most critical step, essential to any study protocol, is the informed consent. During this process, potential participants are given full disclosure of what to expect, the opportunity to ask any questions and a contact name and phone number for any questions that may arise. Prior to initiating any medications, patients must have a complete understanding of the alternatives and very consciously provide informed consent, a formal commitment to participate and adhere. Patients initiating therapy for the first time are generally being prescribed five to fourteen pills per day in their initial regimen. In almost every case, the patient is likely to experience mild to moderate gastrointestinal, dermatologic or central nervous systems side effects at the beginning of therapy.

In an effort to improve drug therapy outcomes, an extension of these rigorous procedures beyond controlled study situations could be employed in clinical practice. HIV pharmacotherapy specialists may be able to re-create the intensity of patient selection, informed consent, medication counselling, monitoring for adverse effects and on-going motivation in general clinical practice to optimize antiretroviral success. A review of the challenges of achieving virologic suppression helps to illustrate the value, and perhaps necessity, of incorporating HIV pharmacotherapists, into the standard care of patients with HIV infection.

Pharmacologic Components of Virologic Success

While the goal of HIV therapy is quite straightforward, successfully reducing viral load to undetectable levels has become increasingly complex. Viral mutations can lead to the development of resistance to potent antiretroviral therapy leading to loss of viral suppression. Treatments can fail leading to resistance for a number of reasons including: poor absorption, prior sub-optimal exposures, drug interactions and non-adherence (2).

Antiretroviral Potency

Table 1 outlines the antiretroviral agents currently available for constructing potent regimens. Although ease of administration, short- and long-term toxicity and virologic resistance are important factors in selecting a first-line regimen, potency remains the primary consideration. While there are many drugs which meet this criterion, considerable controversy exists as to what combination, if any, leads to the best virologic results.

Table 1. The HIV Armamentarium: Currently Marketed Antiretroviral Agents.

Trade Name	Generic Name	Common Adult Doses	# of pills/capsules/day
Nucleoside reverse transcriptase inhibitors (NRTIs)			
Retrovir®	Zidovudine, AZT	300 mg bid	2
Epivir®	Lamivudine, 3TC	150 mg bid	2
Combivir™	AZT + 3TC	1 bid	2
Videx®	Didanosine, ddl	200 mg bid or 400 mg qd	2-4
Hivid®	Zalcitabine, ddC	0.75 mg tid	3
Zerit®	Stavudine, d4T	30-40 mg bid	2
Ziagen™	Abacavir	300 mg bid	2
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)			
Viramune®	Nevirapine	200 mg bid	2
Rescriptor®	Delavirdine	400 mg tid	12
Sustiva™	Efavirenz	600 mg qd	3
Protease inhibitors (PIs)			
Invirase®	Saquinavir (hard cap)	600 mg tid	9
Fortovase™	Saquinavir (soft gel)	1200 mg tid	18
Crixivan®	Indinavir	800 mg tid	6
Norvir™	Ritonavir (caps or liquid)	600 mg bid	12 (15 ml)
Viracept®	Nelfinavir	750 mg tid or 1250 mg bid	9 or 10
Agenerase™	Amprenavir	1200 mg bid	16

The leading national and international panels providing recommendations for initiating therapy give appropriate options to providers but do not recommend a single “best” standard regimen. The recommendations emphasize the need to individualize regimens, accounting for potency, tolerability, adverse effect profiles, drug interactions, convenience and adherence likelihood, and potential for alternative treatment options if the initial regimen fails (1-3).

Use of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse

transcriptase inhibitor (NNRTI) appears to be at least as effective as two NRTIs plus a potent protease inhibitor (PI) (11). Findings to date indicate that PIs and NNRTIs probably produce similar virologic response rates when given as first-line therapy (13).

Alternatively, abacavir plus 2 additional NRTIs, a triple NRTI regimen, has been used with some success (14); however, such a regimen may have short lived efficacy when used in patients with baseline viral loads greater than 100,000 copies/mL. A double-blind, placebo-controlled trial compared abacavir, zidovudine and lamivudine triple nucleoside therapy with a standard PI-containing regimen (indinavir, zidovudine and lamivudine). Antiretroviral-naïve patients who began treatment with a high viral load (above 100,000 copies/mL) had a poorer response with the triple-nucleoside combination after 48 weeks of follow-up (14).

Achieving Adequate Concentrations

With the exception of a few nucleoside analogues which are dosed according to body weight, the majority of antiretrovirals are dosed according to a standard regimen for most patients. These standard regimens are expected to achieve adequate serum concentrations for all patients; however, many factors can contribute to inadequate concentrations of antiretrovirals.

Drug Interactions. Drug interactions can significantly reduce concentrations of antiretrovirals resulting in insufficient inhibition of viral replication. Clinicians need to be aware of concurrent medications (including herbals) and whether any of these drugs are capable of reducing antiretroviral concentrations. Several agents such as rifampin and phenytoin are known to induce hepatic metabolism and should prompt clinicians to adjust doses (15). Unfortunately, formal pharmacokinetic studies have not been performed to elucidate the magnitude of the interactions and guide dose adjustments for many of these well-known inducers. The recent finding that St. John's Wort is capable of reducing indinavir serum concentrations, reinforces the need for complete medication histories to determine non-prescription drug usage and our lack of appreciation of the potential risks with herbals (16). In addition, complex, multidirectional drug interactions, such as those that would be encountered when using a combination of enzyme inducers and enzyme inhibitors (e.g. ritonavir, indinavir, efavirenz), often yield unpredictable results. In the absence of available pharmacokinetic studies to guide dose adjustments, the use of therapeutic drug monitoring has been explored since sub-therapeutic drug concentrations have been shown to be independent predictors of poor viral outcome (17).

Fortunately, favorable drug interactions have been identified which allow maintenance of adequate drug concentrations with lower doses. The use of dual protease inhibitors, particularly those regimens that include the most potent enzyme inhibitor ritonavir, can boost protease inhibitor concentrations, prolong drug half-lives and increase trough concentrations significantly above minimum inhibitory concentrations.

Scheduling. Since mutations to HIV can occur quickly in the presence of sub-optimal antiretroviral exposure, it is imperative to keep antiretroviral concentrations at a critical level. Although appropriate doses of potent antiretroviral agents may be prescribed, taking the correct number of medications at the correct time with the appropriate food and/or beverages is important in maintaining sufficient plasma concentrations throughout an entire dosing interval.

Individual antiretroviral agent pharmacokinetics determines the dosing interval most appropriate for keeping concentrations therapeutic. In light of the minimal pharmacologic forgiveness of most antiretrovirals, the dosing interval cannot be exceeded for extended periods of time without compromising virologic efficacy.

The pharmacokinetic goal with antiretrovirals, particularly protease inhibitors, is to maintain the trough concentration ($C_{\min}$) at the end of the dosing interval above the 90% inhibitory concentration (IC_{90}) and, ideally, well above the IC_{90} . This should prevent virologic breakthrough in an adherent patient. However, if the $C_{\min}$ falls below the IC_{90} , viral replication may begin at the end of the dosing interval. In drugs with very short half-lives, such as indinavir, precise timing of drug administration may be crucial to ensure that concentrations do not remain below the IC_{90} for significant periods.

This prompted the manufacturers of indinavir to recommend dosing the drug precisely every eight

hours instead of approximately three times daily (18). It has now been demonstrated; however, that combining indinavir with ritonavir makes twice-daily indinavir dosing possible, allowing both drugs to be taken concomitantly with meals (19).

Several antiretrovirals, such as didanosine, lamivudine, nevirapine and efavirenz, have half-lives that permit at least twice daily dosing and, in some cases, once daily dosing. In fact, didanosine and efavirenz have indications for once-daily dosing and nevirapine is being evaluated as a possible once-daily medication (20).

In addition to appropriate timing and equal spacing, food and gastric acid requirements must be considered. Both didanosine and indinavir must be administered on an empty stomach; however, they have opposing acid requirements for absorption (18,21). The buffering agent in the didanosine formulation inhibits the absorption of indinavir, which requires an acidic environment. Thus, these two drugs both require consumption on an empty stomach, but cannot be taken within 1-2 hours of each other (22). Drugs such as saquinavir, ritonavir and nelfinavir should be administered with food and drugs such as delavirdine require an acidic gastric environment for optimal absorption (23-26).

Concomitant disease states such as hepatitis or renal disease can also affect drug exposure. For instance, drug malabsorption may occur in patients with severe, continuous diarrhea, while increased drug exposure may occur in patients with impaired hepatic or renal function (27,28).

Adherence

Unfortunately, results from well designed trials and use of potent, strategic antiretroviral regimens are fruitless if the prescribed medications are not being taken correctly by the patient. It has been suggested that greater than 95% adherence to antiretroviral medications is required to achieve satisfactory viral suppression (29). Among patients with 80% to 90% adherence, a 50% failure rate is seen in most trials and in clinical practice (12,29).

Since adherence is affected by a combination of factors, all must be assessed and addressed to optimize disease outcomes and avoid the ultimate consequence of non-adherence - drug failure. Adherence decreases as the number of medications, doses and side effects increase and as competing priorities prevail in a patient's life (30). Further complicating the chronic management of HIV populations are the vast array of social, psychological and cultural issues which are present in an increasing number of patients. These factors are often undisclosed to the physician and therefore not addressed in the context of HIV care. Failure to recognize and address these issues may result in discordance between priorities of patients versus caregivers and subsequent inability to help improve adherence with appropriate measures (31,32). When complex antiretroviral drug therapy is placed into the context of patients who have little financial support and have cultural, social and behavioural barriers to accessing health care, the result is often fragmented, ineffective health care. This may lead to sub-optimal therapeutic response and increased costs. Factors influencing adherence generally can be categorized as patient-related factors, patient-provider factors and clinical factors.

Patient-related Factors

Psychosocial Factors. Much is known regarding clinical factors that can affect adherence; however, patient-specific issues can dramatically compromise adherence (31,33). Studies have identified illicit drug use, alcohol abuse and depression as being predictors of poor adherence (29,33,34). In addition, patients who perceive that the medications will not work or who have had a negative experience in the past tend to adhere less rigorously (33). Before appropriate professionals can adequately address these issues, efforts must be made to identify them. Patient interviews, counselling and a comprehensive, multi-disciplinary assessment of readiness should be undertaken before initiating antiretroviral therapy.

Educational Factors. Patients who perceive the importance of adherence to ensure viral suppression and understand the consequence of non-adherence tend to perform better with respect to pill taking (33). Thus, not only do patients need to fully appreciate the disease, its progression and the role of the medications, they also need to understand the exact way that all of the medications must be administered.

Provider/Healthcare-related Factors

Patients need to feel a sense of trust, open communication and collaboration with their medical and healthcare providers in order to adhere to recommended therapies. There needs to be a feasible mechanism for communication between clinic visits to allow the patient to feel that concerns regarding adverse reactions, social barriers and general questions can be addressed. Patients need to feel that there is collaboration among healthcare providers and that all are striving towards a common goal, most importantly, one that has been agreed to by the patient.

As previously discussed, adherence is vital to the success of any antiretroviral regimen. Accurate assessment of adherence continues to remain an elusive endeavor although patient-reported adherence has been proposed to be a reliable tool (35,36). Although potentially useful in some situations, it has been well documented that self-reported adherence tends to over-estimate true patient adherence (37). In order to maximize the reliability of this highly convenient assessment tool, consistent, trusting, open communication must be established between providers and patients to facilitate honesty and mutual collaboration.

Clinical Factors

Pill Burden. With current multiple-drug regimens, the standard of care being at least triple-therapy, it is not unprecedented, or even unusual, for patients to be ingesting 20 to 30 pills per day. In addition, drugs for opportunistic infection treatment or prophylaxis and non-HIV conditions further contribute to pill burden. The size of the tablets or capsules can also be restrictive and very few of the agents are available as a tolerable liquid.

Dosing Frequency. Not only does scheduling affect achievement of adequate concentrations, it is also a factor in ensuring adherence. Most of the available antiretroviral agents need to be administered multiple times during the day based on their plasma half-life. For patients who have busy schedules, each additional dosing event has the potential to negatively affect adherence (38). Although drugs that only need to be administered once daily are preferred, the pharmacokinetics of currently available agents require multiple administration times each day. At this time, only efavirenz (39) and didanosine are approved for once daily dosing. Since the most commonly cited reason for missing antiretroviral doses is simply forgetting, it is not surprising that with each additional dose needed throughout the day, adherence is compromised (40).

Adverse Effects. As the trend in HIV pharmacotherapy is to treat patients earlier in their disease while they are still relatively asymptomatic, many patients have never experienced adverse events related to their HIV (1). In many cases, with the initiation of antiretroviral therapy, patients experience medication related adverse effects that can have a negative impact on subsequent adherence. Short-term and long-term adverse reactions have been identified with all of the available antiretroviral agents (41). Identification of a growing number of side effects and the realization that disease management is chronic (i.e. life-long), necessitates evaluation of how aggressive pharmacologic therapy should be for each patient, taking into account risks for long-term complications, quality of life and patient desires or priorities. Adverse drug reactions can be early and transient or evident with more prolonged use (from months to years). Both can range from mild to potentially life-threatening. Many are manageable or even avoidable with careful dose adjustment, patient counselling and adjunctive therapies. Since some adverse drug reactions have similar manifestations to HIV-associated symptoms, such as HIV gastropathy and neuropathy, patient complaints should be carefully assessed as to potential etiology before considering modifications to antiretroviral regimens.

Non-nucleoside reverse transcriptase inhibitors (delavirdine, nevirapine and efavirenz) have been associated with dermatologic manifestations (26,39,42). Although the rashes are usually mild to moderate and often can be treated without discontinuation of the medication, life-threatening and fatal rashes have been reported (43). Efavirenz, the newest drug in the class, has been associated with temporarily debilitating central nervous system effects. Patients describe feelings of euphoria or dysphoria, nightmares or vivid dreams, somnolence and dizziness. Most reports are transient, resolving in 1 to 3 weeks (39). Patients must be made aware of potential reactions and informed to contact the provider before discontinuing the therapy on his/her own. In cases where dose

adjustments have been made to account for drug interactions involving the NNRTI, self-discontinuation of the NNRTI without informing the provider can lead to harmful pharmacokinetic results of either sub-optimal exposures or toxicities.

Protease inhibitors, although the most potent class of agents, may be associated with long-term metabolic sequelae, including abnormal fat distribution, glucose intolerance and hyperlipidemias (44-47). Although widely described, the long-term impact of these metabolic effects is unclear. Acutely, the major toxicities associated with protease inhibitors are primarily related to the gastrointestinal system, although hepatitis, hyperbilirubinemia, nephrolithiasis, dermatological manifestations and paresthesias have been reported (18,23-25,48,49).

Nucleoside analogues are often associated with more systemic and constitutional side effects such as nausea, vomiting, headache and anemias although they also can be associated with painful and potentially irreversible peripheral neuropathies, particularly with didanosine and stavudine (50, 51). Abacavir, the most recently marketed nucleoside analogue, has also been associated with a potentially fatal skin rash which tends to manifest along with systemic effects such as nausea, fatigue and fever. Re-challenge of patients experiencing these effects with abacavir is contra-indicated (52). Nucleoside reverse transcriptase inhibitors (NRTI) have become associated with a side effect termed "mitochondrial toxicity", which can manifest as simply mild peripheral neuropathy to life-threatening lactic acidosis. Although lactic acidosis remains a rare complication of NRTI therapy, it can be associated with significant morbidity and mortality. Screening methods to detect mitochondrial toxicity need to be identified to avoid the development of life-threatening lactic acidosis (53).

Although the majority of adverse effects are transient and manageable, many patients discontinue them without communication with their provider, leading to potential complications of disease management with consequences to future treatment options. When patients are not expecting the side effects or are not equipped to deal with them, adherence can be compromised by the drug-related disturbances.

Pharmacotherapy Management Strategies: HIV Pharmacotherapy Specialists

The ability of current antiretroviral regimens to be potent enough to maintain control of the virus depends on a degree of adherence not required for any other disease state to date. Unfortunately, the 95% degree of adherence likely required is something that most patients cannot achieve. Therefore, new practice models are required to assist patients in achieving sufficient adherence for reaching undetectable viral loads.

Emerging Roles for HIV Pharmacotherapy Specialists

HIV pharmacotherapy specialists are in a unique position to impact virologic outcomes in antiretroviral therapy. With advanced training, they can become experts in the integration of drug and non-drug contributors to therapeutic success or failure. They are able to assess adherence, potential drug-related toxicities and drug-drug or drug-food interactions, all factors vital to ensuring antiviral success. The interface of antiretroviral pharmacokinetics and pharmacodynamics are critical to optimizing therapeutic regimens and can be addressed by pharmacotherapists with appropriate expertise. Additionally, the management of non-HIV associated pharmacotherapy (e.g. optimizing antihypertensive therapies), management of drug toxicities (e.g. peripheral neuropathies) and disease manifestations such as hyperlipidemia or diabetes in the face of HIV can require complex assessments, dosing recommendations, monitoring and labour-intensive counselling.

Pharmacists have been providing pharmaceutical care in HIV to varying degrees since early in the epidemic; however, recently, more elaborate models of practice have been implemented. Although some programs utilize pharmacists simply for the drug therapy education (54), others prospectively monitor for drug related problems. (55-61). In attempts to coordinate patient care, specifically with respect to pharmacotherapy, seamless pharmaceutical care model programs have been successfully developed to integrate inpatient and outpatient needs for patients with HIV (55).

Pharmacists are documenting activities to enhance adherence such as providing written, individualized medication schedules, organizing and/or pre-filling pill boxes, giving out beepers (62),

telephone follow-up (60) and management of side effects associated with new antiretroviral regimens (57,58,60,62,63). Pharmacists are commonly required to adjust doses and intervene on potentially significant drug interactions (58,62,64,65).

Since concentration-effect relationships have been identified with many antiretroviral agents, there has been some interest in the clinical utility of monitoring protease inhibitor concentrations to optimize antiretroviral therapy (17,66,67). Since interpretation of these concentrations remains challenging, comprehensive pharmacologic assessments concurrent with evaluation of concentrations is essential. A pharmacy-based program has been developed to integrate the evaluation of adherence and simultaneous assessment of toxicity and drug interactions with therapeutic drug monitoring (67).

Programs are beginning to surface that provide innovative models for integrating patient adherence assessment with pharmacokinetic, pharmacodynamic and virologic outcome analysis (58,68-70). Preliminary evidence suggests that interventions by HIV pharmacotherapists can improve the virologic outcomes in patients on antiretroviral therapy. The impact of pharmacists' adherence interventions in a group of patients failing antiretroviral therapy due to suspected non-adherence was evaluated (69). Of patients who remained on a failing antiretroviral regimen, 36% eventually demonstrated a clinically significant viral response in the absence of a medication change. All of these patients had received adherence assessments and enhancement sessions with an HIV pharmacotherapist.

In a group of antiretroviral naïve patients started on therapy with the assistance of an HIV pharmacotherapist, a significantly increased number of patients were able to reach an undetectable viral load compared with a control group who did not receive the same intensity of pharmaceutical care (70).

Conclusion

The progression in antiretroviral therapy to complex, chronic regimens has made pharmacologic assessment of the patient an important aspect of chronic HIV management. HIV pharmacotherapists can be highly qualified to evaluate patients with complex drug regimens who are facing barriers to successful care, to target the appropriate intervention(s) and follow-up with the patients on a long-term basis. Emerging models demonstrating the expertise of pharmacotherapy specialists may show that a great deal more than choosing potent antiretrovirals is need to ensure desired outcomes.

Post-graduate training opportunities exist in HIV pharmacotherapy in the form of specialty residencies, fellowships, preceptorships and certificate programs (<http://www.tthivclinic.com/>). Additionally, on-line resources and websites are available to link HIV pharmacotherapy providers and provide educational, clinical and research-directed supports (<http://www.hiv.buffalo.edu/>).

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Issues in Human Immunodeficiency Virus (HIV) Pharmacotherapy Practice: The Emerging Role of Pharmacotherapy Specialists in Enhancing Antiretroviral Success

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Human immunodeficiency virus (HIV) pharmacotherapy has evolved into a highly complex clinical specialty requiring a delicate balance of art and science to achieve and maintain the therapeutic goals of complete viral suppression while maintaining quality of life. The complexity of the inter-relationship between the virology, pharmacology, pharmacokinetics, pharmacodynamics and patient-related factors creates a sizeable therapeutic challenge. Adherence to prescribed antiretrovirals remains the ultimate challenge as it has been shown that near perfect adherence is required to achieve adequate and sustained viral suppression. Innovative changes in clinical practice models have been proposed and implemented in an attempt to incorporate multiple disciplines for optimal patient management. The role of HIV pharmacotherapy specialists is evolving and may be paramount to successful antiretroviral management in this specialty arena. A review of the challenges of achieving virologic suppression clearly illustrates the value, and perhaps necessity, of incorporating HIV pharmacotherapists into the standard care of patients with HIV infection.

J Inform Pharmacother 2001;4:306-316.

Significant advances in HIV pharmacotherapy include the enhanced understanding of viral replication in the human host, the ability to quantify viral load and correlate with clinical outcomes, the availability of tools to assess viral susceptibility, the development of new antiretroviral agents and a heightened appreciation of the importance of patient adherence to prescribed antiretroviral regimens to ensure successful virologic suppression (1). Despite advances and the availability of several sets of state-of-the-art treatment guidelines, no overall consensus

has emerged with respect to when to initiate therapy and which agents to use to maximize virologic suppression (1-3). Most authorities would agree; however, that left untreated, viral replication causes life-threatening destruction of the immune system and the development of more genetically diverse and increasingly virulent strains, due to this highly mutable virus. Thus, complex antiretroviral regimens are necessary in most patients infected with HIV. Although many regimens appear effective, the optimal regimen or protocol to employ when initiating antiretroviral therapy remains unclear.

The goal of this paper is to describe the current standards of HIV care and the complexities and challenges that exist in effectively implementing these standards. The emerging role of HIV pharmacotherapy specialists (pharmacists specializing in clinical HIV care) in enhancing antiretroviral success will be discussed.

Disparity Between Efficacy and Effectiveness

Initiation of potent antiretroviral therapy has improved virologic and clinical outcomes of patients with HIV infection, such as decreasing incidence of opportunistic infections, hospitalizations and mortality (4,5). In vivo studies have provided data regarding the efficacy of new agents and new therapeutic combinations of antiretrovirals. In clinical trials, various combinations of protease inhibitors, nucleoside analogues and/or non-nucleoside reverse transcriptase inhibitors have reduced plasma HIV-1 RNA levels to less than 500 copies/mL in 60% to 90% of antiretroviral-naïve patients (6-11).

Of concern; however, is that the true effectiveness of these drugs (i.e. their benefits in routine clinical

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use) has been less than expected based on the results of the original clinical trials. In an urban HIV clinic, Lucas et al. found that less than 43% of previously antiretroviral-naïve patients who initiated therapy with one of these agents had an undetectable viral load at 3 months, 48.8% were undetectable at 3-7 months and only 38.4% were undetectable at 7-14 months (12). This falls far short of the therapeutic goal of 100% viral suppression and the 60-90% undetectable viral load rates reported in earlier clinical trials.

It would appear that once out of the rigors of participation in a clinical trial, with recruitment of only the most motivated, “ideal” patients, consistent counselling related to the study medications and regulated monitoring and follow-up, the effectiveness of antiretroviral agents is diminished. In clinical studies, there is typically a close evaluation of patients’ lifestyles prior to recruitment to ensure that non-medical issues such as language barriers, childcare issues and employment barriers will not interfere with the study protocol. In addition, baseline physical exams aim to identify or rule out any pre-existing medical conditions that may be exacerbated by the introduction of the new medications or at least serve as a complete baseline to enable adequate assessment of any newly identified drug-related problems. Careful scrutiny of concomitant medication use minimizes the likelihood that drug interactions will interfere with the safety and/or efficacy of the new medications. Perhaps the most critical step, essential to any study protocol, is the informed consent. During this process, potential participants are given full disclosure of what to expect, the opportunity to ask any questions and a contact name and phone number for any questions that may arise. Prior to initiating any medications, patients must have a complete understanding of the alternatives and very consciously provide informed consent, a formal commitment to participate and adhere. Patients initiating therapy for the first time are generally being prescribed five to fourteen pills per day in their initial regimen. In almost every case, the patient is likely to experience mild to moderate gastrointestinal, dermatologic or central nervous systems side effects at the beginning of therapy.

In an effort to improve drug therapy outcomes, an extension of these rigorous procedures beyond controlled study situations could be employed in

clinical practice. HIV pharmacotherapy specialists may be able to re-create the intensity of patient selection, informed consent, medication counselling, monitoring for adverse effects and on-going motivation in general clinical practice to optimize antiretroviral success. A review of the challenges of achieving virologic suppression helps to illustrate the value, and perhaps necessity, of incorporating HIV pharmacotherapists, into the standard care of patients with HIV infection.

Pharmacologic Components of Virologic Success

While the goal of HIV therapy is quite straightforward, successfully reducing viral load to undetectable levels has become increasingly complex. Viral mutations can lead to the development of resistance to potent antiretroviral therapy leading to loss of viral suppression. Treatments can fail leading to resistance for a number of reasons including: poor absorption, prior sub-optimal exposures, drug interactions and non-adherence (2).

Antiretroviral Potency

Table 1 outlines the antiretroviral agents currently available for constructing potent regimens. Although ease of administration, short- and long-term toxicity and virologic resistance are important factors in selecting a first-line regimen, potency remains the primary consideration. While there are many drugs which meet this criterion, considerable controversy exists as to what combination, if any, leads to the best virologic results.

The leading national and international panels providing recommendations for initiating therapy give appropriate options to providers but do not recommend a single “best” standard regimen. The recommendations emphasize the need to individualize regimens, accounting for potency, tolerability, adverse effect profiles, drug interactions, convenience and adherence likelihood, and potential for alternative treatment options if the initial regimen fails (1-3).

Use of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse

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Table 1. The HIV Armamentarium: Currently Marketed Antiretroviral Agents.

Trade Name	Generic Name	Common Adult Doses	# of pills/capsules/day
Nucleoside reverse transcriptase inhibitors (NRTIs)			
Retrovir®	Zidovudine, AZT	300 mg bid	2
Epivir®	Lamivudine, 3TC	150 mg bid	2
Combivir™	AZT + 3TC	1 bid	2
Videx®	Didanosine, ddi	200 mg bid or 400 mg qd	2-4
Hivid®	Zalcitabine, ddC	0.75 mg tid	3
Zerit®	Stavudine, d4T	30-40 mg bid	2
Ziagen™	Abacavir	300 mg bid	2
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)			
Viramune®	Nevirapine	200 mg bid	2
Rescriptor®	Delavirdine	400 mg tid	12
Sustiva™	Efavirenz	600 mg qd	3
Protease inhibitors (PIs)			
Invirase®	Saquinavir (hard cap)	600 mg tid	9
Fortovase™	Saquinavir (soft gel)	1200 mg tid	18
Crixivan®	Indinavir	800 mg tid	6
Norvir™	Ritonavir (caps or liquid)	600 mg bid	12 (15 ml)
Viracept®	Nelfinavir	750 mg tid or 1250 mg bid	9 or 10
Agenerase™	Amprenavir	1200 mg bid	16

transcriptase inhibitor (NNRTI) appears to be at least as effective as two NRTIs plus a potent protease inhibitor (PI) (11). Findings to date indicate that PIs and NNRTIs probably produce similar virologic response rates when given as first-line therapy (13).

Alternatively, abacavir plus 2 additional NRTIs, a triple NRTI regimen, has been used with some success (14); however, such a regimen may have short lived efficacy when used in patients with baseline viral loads greater than 100,000 copies/mL. A double-blind, placebo-controlled trial compared abacavir, zidovudine and lamivudine triple nucleoside therapy with a standard PI-containing regimen (indinavir, zidovudine and lamivudine). Antiretroviral-naïve patients who began treatment with a high viral load (above 100,000 copies/mL) had a poorer response with the triple-nucleoside combination after 48 weeks of follow-up (14).

Achieving Adequate Concentrations

With the exception of a few nucleoside analogues which are dosed according to body weight, the

majority of antiretrovirals are dosed according to a standard regimen for most patients. These standard regimens are expected to achieve adequate serum concentrations for all patients; however, many factors can contribute to inadequate concentrations of antiretrovirals.

Drug Interactions. Drug interactions can significantly reduce concentrations of antiretrovirals resulting in insufficient inhibition of viral replication. Clinicians need to be aware of concurrent medications (including herbals) and whether any of these drugs are capable of reducing antiretroviral concentrations. Several agents such as rifampin and phenytoin are known to induce hepatic metabolism and should prompt clinicians to adjust doses (15). Unfortunately, formal pharmacokinetic studies have not been performed to elucidate the magnitude of the interactions and guide dose adjustments for many of these well-known inducers. The recent finding that St. John's Wort is capable of reducing indinavir serum concentrations, reinforces the need for complete medication histories to determine non-prescription drug usage and our lack of appreciation of the

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potential risks with herbals (16). In addition, complex, multidirectional drug interactions, such as those that would be encountered when using a combination of enzyme inducers and enzyme inhibitors (e.g. ritonavir, indinavir, efavirenz), often yield unpredictable results. In the absence of available pharmacokinetic studies to guide dose adjustments, the use of therapeutic drug monitoring has been explored since sub-therapeutic drug concentrations have been shown to be independent predictors of poor viral outcome (17).

Fortunately, favorable drug interactions have been identified which allow maintenance of adequate drug concentrations with lower doses. The use of dual protease inhibitors, particularly those regimens that include the most potent enzyme inhibitor ritonavir, can boost protease inhibitor concentrations, prolong drug half-lives and increase trough concentrations significantly above minimum inhibitory concentrations.

Scheduling. Since mutations to HIV can occur quickly in the presence of sub-optimal antiretroviral exposure, it is imperative to keep antiretroviral concentrations at a critical level. Although appropriate doses of potent antiretroviral agents may be prescribed, taking the correct number of medications at the correct time with the appropriate food and/or beverages is important in maintaining sufficient plasma concentrations throughout an entire dosing interval.

Individual antiretroviral agent pharmacokinetics determines the dosing interval most appropriate for keeping concentrations therapeutic. In light of the minimal pharmacologic forgiveness of most antiretrovirals, the dosing interval cannot be exceeded for extended periods of time without compromising virologic efficacy.

The pharmacokinetic goal with antiretrovirals, particularly protease inhibitors, is to maintain the trough concentration (C_{min}) at the end of the dosing interval above the 90% inhibitory concentration (IC_{90}) and, ideally, well above the IC_{90} . This should prevent virologic breakthrough in an adherent patient. However, if the C_{min} falls below the IC_{90} , viral replication may begin at the end of the dosing interval. In drugs with very short half-lives, such as indinavir, precise timing of drug administration may

be crucial to ensure that concentrations do not remain below the IC_{90} for significant periods. This prompted the manufacturers of indinavir to recommend dosing the drug precisely every eight hours instead of approximately three times daily (18). It has now been demonstrated; however, that combining indinavir with ritonavir makes twice-daily indinavir dosing possible, allowing both drugs to be taken concomitantly with meals (19).

Several antiretrovirals, such as didanosine, lamivudine, nevirapine and efavirenz, have half-lives that permit at least twice daily dosing and, in some cases, once daily dosing. In fact, didanosine and efavirenz have indications for once-daily dosing and nevirapine is being evaluated as a possible once-daily medication (20).

In addition to appropriate timing and equal spacing, food and gastric acid requirements must be considered. Both didanosine and indinavir must be administered on an empty stomach; however, they have opposing acid requirements for absorption (18,21). The buffering agent in the didanosine formulation inhibits the absorption of indinavir, which requires an acidic environment. Thus, these two drugs both require consumption on an empty stomach, but cannot be taken within 1-2 hours of each other (22). Drugs such as saquinavir, ritonavir and nelfinavir should be administered with food and drugs such as delavirdine require an acidic gastric environment for optimal absorption (23-26).

Concomitant disease states such as hepatitis or renal disease can also affect drug exposure. For instance, drug malabsorption may occur in patients with severe, continuous diarrhea, while increased drug exposure may occur in patients with impaired hepatic or renal function (27,28).

Adherence

Unfortunately, results from well designed trials and use of potent, strategic antiretroviral regimens are fruitless if the prescribed medications are not being taken correctly by the patient. It has been suggested that greater than 95% adherence to antiretroviral medications is required to achieve satisfactory viral suppression (29). Among patients with 80% to 90%

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adherence, a 50% failure rate is seen in most trials and in clinical practice (12,29).

Since adherence is affected by a combination of factors, all must be assessed and addressed to optimize disease outcomes and avoid the ultimate consequence of non-adherence - drug failure. Adherence decreases as the number of medications, doses and side effects increase and as competing priorities prevail in a patient's life (30). Further complicating the chronic management of HIV populations are the vast array of social, psychological and cultural issues which are present in an increasing number of patients. These factors are often undisclosed to the physician and therefore not addressed in the context of HIV care. Failure to recognize and address these issues may result in discordance between priorities of patients versus caregivers and subsequent inability to help improve adherence with appropriate measures (31,32). When complex antiretroviral drug therapy is placed into the context of patients who have little financial support and have cultural, social and behavioural barriers to accessing health care, the result is often fragmented, ineffective health care. This may lead to sub-optimal therapeutic response and increased costs. Factors influencing adherence generally can be categorized as patient-related factors, patient-provider factors and clinical factors.

Patient-related Factors

Psychosocial Factors. Much is known regarding clinical factors that can affect adherence; however, patient-specific issues can dramatically compromise adherence (31,33). Studies have identified illicit drug use, alcohol abuse and depression as being predictors of poor adherence (29,33,34). In addition, patients who perceive that the medications will not work or who have had a negative experience in the past tend to adhere less rigorously (33). Before appropriate professionals can adequately address these issues, efforts must be made to identify them. Patient interviews, counselling and a comprehensive, multi-disciplinary assessment of readiness should be undertaken before initiating antiretroviral therapy.

Educational Factors. Patients who perceive the importance of adherence to ensure viral suppression and understand the consequence of non-adherence tend to perform better with respect to pill taking

(33). Thus, not only do patients need to fully appreciate the disease, its progression and the role of the medications, they also need to understand the exact way that all of the medications must be administered.

Provider/Healthcare-related Factors

Patients need to feel a sense of trust, open communication and collaboration with their medical and healthcare providers in order to adhere to recommended therapies. There needs to be a feasible mechanism for communication between clinic visits to allow the patient to feel that concerns regarding adverse reactions, social barriers and general questions can be addressed. Patients need to feel that there is collaboration among healthcare providers and that all are striving towards a common goal, most importantly, one that has been agreed to by the patient.

As previously discussed, adherence is vital to the success of any antiretroviral regimen. Accurate assessment of adherence continues to remain an elusive endeavor although patient-reported adherence has been proposed to be a reliable tool (35,36). Although potentially useful in some situations, it has been well documented that self-reported adherence tends to over-estimate true patient adherence (37). In order to maximize the reliability of this highly convenient assessment tool, consistent, trusting, open communication must be established between providers and patients to facilitate honesty and mutual collaboration.

Clinical Factors

Pill Burden. With current multiple-drug regimens, the standard of care being at least triple-therapy, it is not unprecedented, or even unusual, for patients to be ingesting 20 to 30 pills per day. In addition, drugs for opportunistic infection treatment or prophylaxis and non-HIV conditions further contribute to pill burden. The size of the tablets or capsules can also be restrictive and very few of the agents are available as a tolerable liquid.

Dosing Frequency. Not only does scheduling affect achievement of adequate concentrations, it is also a factor in ensuring adherence. Most of the available

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antiretroviral agents need to be administered multiple times during the day based on their plasma half-life. For patients who have busy schedules, each additional dosing event has the potential to negatively affect adherence (38). Although drugs that only need to be administered once daily are preferred, the pharmacokinetics of currently available agents require multiple administration times each day. At this time, only efavirenz (39) and didanosine are approved for once daily dosing. Since the most commonly cited reason for missing antiretroviral doses is simply forgetting, it is not surprising that with each additional dose needed throughout the day, adherence is compromised (40).

Adverse Effects. As the trend in HIV pharmacotherapy is to treat patients earlier in their disease while they are still relatively asymptomatic, many patients have never experienced adverse events related to their HIV (1). In many cases, with the initiation of antiretroviral therapy, patients experience medication related adverse effects that can have a negative impact on subsequent adherence. Short-term and long-term adverse reactions have been identified with all of the available antiretroviral agents (41). Identification of a growing number of side effects and the realization that disease management is chronic (i.e. life-long), necessitates evaluation of how aggressive pharmacologic therapy should be for each patient, taking into account risks for long-term complications, quality of life and patient desires or priorities. Adverse drug reactions can be early and transient or evident with more prolonged use (from months to years). Both can range from mild to potentially life-threatening. Many are manageable or even avoidable with careful dose adjustment, patient counselling and adjunctive therapies. Since some adverse drug reactions have similar manifestations to HIV-associated symptoms, such as HIV gastropathy and neuropathy, patient complaints should be carefully assessed as to potential etiology before considering modifications to antiretroviral regimens.

Non-nucleoside reverse transcriptase inhibitors (delavirdine, nevirapine and efavirenz) have been associated with dermatologic manifestations (26,39,42). Although the rashes are usually mild to moderate and often can be treated without discontinuation of the medication, life-threatening and fatal rashes have been reported (43). Efavirenz, the newest drug in the class, has been associated with

temporarily debilitating central nervous system effects. Patients describe feelings of euphoria or dysphoria, nightmares or vivid dreams, somnolence and dizziness. Most reports are transient, resolving in 1 to 3 weeks (39). Patients must be made aware of potential reactions and informed to contact the provider before discontinuing the therapy on his/her own. In cases where dose adjustments have been made to account for drug interactions involving the NNRTI, self-discontinuation of the NNRTI without informing the provider can lead to harmful pharmacokinetic results of either sub-optimal exposures or toxicities.

Protease inhibitors, although the most potent class of agents, may be associated with long-term metabolic sequelae, including abnormal fat distribution, glucose intolerance and hyperlipidemias (44-47). Although widely described, the long-term impact of these metabolic effects is unclear. Acutely, the major toxicities associated with protease inhibitors are primarily related to the gastrointestinal system, although hepatitis, hyperbilirubinemia, nephrolithiasis, dermatological manifestations and paresthesias have been reported (18,23-25,48,49).

Nucleoside analogues are often associated with more systemic and constitutional side effects such as nausea, vomiting, headache and anemias although they also can be associated with painful and potentially irreversible peripheral neuropathies, particularly with didanosine and stavudine (50, 51). Abacavir, the most recently marketed nucleoside analogue, has also been associated with a potentially fatal skin rash which tends to manifest along with systemic effects such as nausea, fatigue and fever. Re-challenge of patients experiencing these effects with abacavir is contra-indicated (52). Nucleoside reverse transcriptase inhibitors (NRTI) have become associated with a side effect termed "mitochondrial toxicity", which can manifest as simply mild peripheral neuropathy to life-threatening lactic acidosis. Although lactic acidosis remains a rare complication of NRTI therapy, it can be associated with significant morbidity and mortality. Screening methods to detect mitochondrial toxicity need to be identified to avoid the development of life-threatening lactic acidosis (53).

Although the majority of adverse effects are transient and manageable, many patients discontinue

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them without communication with their provider, leading to potential complications of disease management with consequences to future treatment options. When patients are not expecting the side effects or are not equipped to deal with them, adherence can be compromised by the drug-related disturbances.

Pharmacotherapy Management Strategies: HIV Pharmacotherapy Specialists

The ability of current antiretroviral regimens to be potent enough to maintain control of the virus depends on a degree of adherence not required for any other disease state to date. Unfortunately, the 95% degree of adherence likely required is something that most patients cannot achieve. Therefore, new practice models are required to assist patients in achieving sufficient adherence for reaching undetectable viral loads.

Emerging Roles for HIV Pharmacotherapy Specialists

HIV pharmacotherapy specialists are in a unique position to impact virologic outcomes in antiretroviral therapy. With advanced training, they can become experts in the integration of drug and non-drug contributors to therapeutic success or failure. They are able to assess adherence, potential drug-related toxicities and drug-drug or drug-food interactions, all factors vital to ensuring antiviral success. The interface of antiretroviral pharmacokinetics and pharmacodynamics are critical to optimizing therapeutic regimens and can be addressed by pharmacotherapists with appropriate expertise. Additionally, the management of non-HIV associated pharmacotherapy (e.g. optimizing antihypertensive therapies), management of drug toxicities (e.g. peripheral neuropathies) and disease manifestations such as hyperlipidemia or diabetes in the face of HIV can require complex assessments, dosing recommendations, monitoring and labour-intensive counselling.

Pharmacists have been providing pharmaceutical care in HIV to varying degrees since early in the epidemic; however, recently, more elaborate models

of practice have been implemented. Although some programs utilize pharmacists simply for the drug therapy education (54), others prospectively monitor for drug related problems. (55-61). In attempts to coordinate patient care, specifically with respect to pharmacotherapy, seamless pharmaceutical care model programs have been successfully developed to integrate inpatient and outpatient needs for patients with HIV (55).

Pharmacists are documenting activities to enhance adherence such as providing written, individualized medication schedules, organizing and/or pre-filling pill boxes, giving out beepers (62), telephone follow-up (60) and management of side effects associated with new antiretroviral regimens (57,58,60,62,63). Pharmacists are commonly required to adjust doses and intervene on potentially significant drug interactions (58,62,64,65).

Since concentration-effect relationships have been identified with many antiretroviral agents, there has been some interest in the clinical utility of monitoring protease inhibitor concentrations to optimize antiretroviral therapy (17,66,67). Since interpretation of these concentrations remains challenging, comprehensive pharmacologic assessments concurrent with evaluation of concentrations is essential. A pharmacy-based program has been developed to integrate the evaluation of adherence and simultaneous assessment of toxicity and drug interactions with therapeutic drug monitoring (67).

Programs are beginning to surface that provide innovative models for integrating patient adherence assessment with pharmacokinetic, pharmacodynamic and virologic outcome analysis (58,68-70). Preliminary evidence suggests that interventions by HIV pharmacotherapists can improve the virologic outcomes in patients on antiretroviral therapy. The impact of pharmacists' adherence interventions in a group of patients failing antiretroviral therapy due to suspected non-adherence was evaluated (69). Of patients who remained on a failing antiretroviral regimen, 36% eventually demonstrated a clinically significant viral response in the absence of a medication change. All of these patients had received adherence assessments and enhancement sessions with an HIV pharmacotherapist.

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In a group of antiretroviral naïve patients started on therapy with the assistance of an HIV pharmacotherapist, a significantly increased number of patients were able to reach an undetectable viral load compared with a control group who did not receive the same intensity of pharmaceutical care (70).

Conclusion

The progression in antiretroviral therapy to complex, chronic regimens has made pharmacologic assessment of the patient an important aspect of chronic HIV management. HIV pharmacotherapists can be highly qualified to evaluate patients with complex drug regimens who are facing barriers to successful care, to target the appropriate intervention(s) and follow-up with the patients on a long-term basis. Emerging models demonstrating the expertise of pharmacotherapy specialists may show that a great deal more than choosing potent antiretrovirals is need to ensure desired outcomes.

Post-graduate training opportunities exist in HIV pharmacotherapy in the form of specialty residencies, fellowships, preceptorships and certificate programs (<http://www.tthivclinic.com/>). Additionally, on-line resources and websites are available to link HIV pharmacotherapy providers and provide educational, clinical and research-directed supports (<http://www.hiv.buffalo.edu/>).

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Research Abstracts

The Journal of Informed Pharmacotherapy 2001;4:400.

An evaluation of the anti-aggressive effects of olanzapine in chronic psychotic patients

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Context

Recent studies have demonstrated that clozapine (CLZ), a novel antipsychotic, effectively reduces aggressive and violent behavior in patients with schizophrenia. However, the exact neurobiology of aggression remains unclear. Several receptor systems have been linked with violence, in particular serotonergic and noradrenergic. The selective effects of clozapine on serotonin and noradrenaline (or dopamine) receptors may partially explain its anti-aggressive properties.

Olanzapine (OLZ) shares a similar pharmacology with clozapine. Both are potent antagonists of 5-HT_{2A}, 2C, 3, 6. In contrast, these agents have different affinities for the 5-HT₇ receptors, with olanzapine being less potent. At dopamine receptors, namely D₁₋₄, olanzapine is consistently more potent than clozapine. Olanzapine is less potent at α -adrenergic receptors. The clinical impact of these pharmacologic similarities and differences has not yet been evaluated with respect to aggression and violence among patients with chronic psychotic disorders.

Objectives

To determine if OLZ effectively reduces aggressive or violent behavior in patients suffering from chronic psychotic disorders.

Setting

A Canadian psychiatric care teaching hospital.

Design

This was a retrospective, mirror image chart review. Sixty-five inpatients of the Nova Scotia Hospital's Rehabilitation and Forensic units, diagnosed with a chronic psychotic disorder, who had received OLZ therapy for >30 days were selected. Time spent in seclusion, prn medication use and behavioral problems were recorded over six months prior to and seven months following the initiation of OLZ treatment. Time spent in seclusion was the primary endpoint. Similar data were collected from 30 patients treated with CLZ for >30 days as a means to validate our methods and results.

Main Outcome Measures

The primary endpoint was the time the patients spent in seclusion.

Results

Time spent in seclusion decreased non-significantly by 10.5 ± 56.3 hours/30 days ($n=33$, $p=0.14$) after starting OLZ therapy. There was a significant improvement in non-compliance (-0.77 ± 2.53 incidents/30 days, $n=65$, $p=0.02$), use of prn benzodiazepines (-35.90 ± 141.51 mg equivalents/30 days, $n=65$, $p=0.045$), use of prn chloral hydrate (-537.21 ± 2057.89 mg chloral hydrate/30 days, $n=65$, $p=0.04$), overall prn medication use (-3.24 ± 7.75 days prn given/30days, $n=57$, $p=0.004$), and overall behavioral incidents (-10.76 ± 9.45 , $n=65$, $p=0.026$). The reduction in agitation (-6.30 ± 25.63 incidents/30 days, $p=0.052$, $n=65$) and verbal aggression (-1.57 ± 6.54 incidents/30 days, $p=0.057$, $n=65$) with OLZ treatment trended towards significance. Findings of reduced seclusion time, prn medication use and behavioural incidents with CLZ were consistent with findings of other investigators and provide validation for our methods.

Conclusions

Switching to OLZ was associated with a significant reduction in overall behavior problems, and specifically non-compliance. PRN benzodiazepine and overall prn medication use also decreased significantly. Time spent in seclusion, agitation and physical aggression decreased non-significantly. Major limitations include regression to the mean bias and uncertainty around point estimates related to the small sample. As far as we are aware this is the first specific examination of the anti-aggressive effects of OLZ in chronic psychosis, other than through sub-factor analysis of the Positive and Negative Symptoms Scale in prospective RCTs. This information is complementary as it reflects real-world use of OLZ in this population. Similar studies to ours that address the anti-aggressive effects of CLZ have been published.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2001;4:401.

Evaluation of timeliness, appropriateness, and efficacy/toxicity of thrombolytic therapy for myocardial infarction

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Context

The American College of Cardiology/American Heart Association (ACC/AHA) has established guidelines for the use of thrombolytic therapy in acute myocardial infarction (AMI). Compliance with these guidelines at our institution is unknown.

Objectives

The objective of this study was to evaluate the timeliness and appropriateness of thrombolytic therapy for AMI and to characterize its efficacy and toxicity.

Setting

Emergency Department (ED) of a large Canadian community hospital.

Design

Retrospective chart review between September 1, 1998 and August 31, 1999. Subjects were patients who received thrombolytic therapy for AMI.

Main Outcome Measures

Five endpoints were examined: *timeliness*, measured by door-to-needle time (DTNT), door-to-data time, data-to-decision time, and decision-to-drug time; *appropriateness* of thrombolysis and of choice

of thrombolytic agent as per the ACC/AHA guidelines; efficacy, defined as the absence of death, need for urgent revascularization, and extension of infarct or reinfarction following thrombolytic therapy; and *toxicity*, the occurrence of an allergic reaction, hypotension, major bleed, or minor bleed.

Results

Sixty-four patients were included. The median DTNT was 43 minutes. The recommended DTNT of <30 minutes was achieved in 28% of patients. The median door-to-data time was 8 minutes, which is within the recommended interval of 10 minutes. The decision time was not documented in charts. The data-to-drug time was found to be 30 minutes. Thrombolytics were indicated in all cases. The ratio of use of tissue plasminogen activator (t-PA) to streptokinase (SK) was 53:47. SK was chosen appropriately in all cases. SK could have been used in 15% of patients treated with t-PA. Thrombolytic therapy was efficacious in 87% of patients. There were no allergic reactions. Hypotension occurred in 5 patients treated with each t-PA and SK. Minor bleeds occurred in 7 and 4 patients and major bleeds in 2 and 1 patients treated with t-PA and SK respectively.

Conclusions

The appropriateness and particularly the timeliness of thrombolysis for AMI in the ED at this hospital needs to be improved.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2001;4:402.

Dextromethorphan: A review of its use in the management of chronic pain

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Context

Allodynia and hyperalgesia of the central nervous system are thought to result from the activation of N-methyl-D-aspartate (NMDA) receptors. The oral antitussive, dextromethorphan, is a readily available NMDA receptor antagonist known to inhibit wind-up and central hyperexcitability of dorsal horn neurons.

Objectives

The objective of this study was to determine the efficacy, safety and toxicity of dextromethorphan in the management of chronic pain.

Setting

A Canadian adult teaching hospital.

Design

A retrospective chart review and follow-up study conducted from June 1999 to June 2000.

Main Outcome Measures

Primary endpoints included pain control assessed on a 0 to 5 point pain scale and adverse events associated with dextromethorphan.

Results

Twenty-four patients prescribed dextromethorphan as an outpatient for the management of chronic pain were identified and evaluated. Fibromyalgia was the primary indication for dextromethorphan in these patients. The average daily maintenance dose of dextromethorphan prescribed was 150-200mg/day. Six patients were followed over a 12 month period. Data on compliance, efficacy and adverse effects experienced with dextromethorphan were tabulated. Using a 0 to 5 point pain scale, pain was assessed at three month intervals by the patient for a two week period and by a telephone interview conducted by the investigator. Three patients discontinued dextromethorphan after three, four and five months respectively with no improvement in pain control. For those whose pain responded to dextromethorphan, pain scoring decreased an average of one level on a 0 to 5 point pain scale. Patients commonly reported that dextromethorphan did not eliminate pain, but made it more tolerable. Patients noted increased mobility, improved sleep and overall management of pain. Side effects were frequent, but acceptable to the patient.

Conclusions

Dextromethorphan should be reserved as an adjunct for chronic pain associated with fibromyalgia where all other therapies have failed.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2001;4:403

Efficacy, safety and cost of intravenous procainamide versus intravenous amiodarone in the treatment of acute onset atrial fibrillation

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Context

Intravenous amiodarone is widely used for the treatment of acute onset atrial fibrillation despite the lack of prospective, randomized, controlled trials supporting its efficacy. The use of intravenous amiodarone at our hospital has almost doubled in the last three years and has been associated with a concurrent increase in drug costs. Intravenous procainamide, which has been shown to be effective in the treatment of acute onset atrial fibrillation in uncontrolled trials, is the only other intravenous antiarrhythmic readily available in Canada for this patient population.

Objectives

The objective of this study was to compare the efficacy, safety, and cost of intravenous amiodarone and intravenous procainamide in the treatment of acute onset atrial fibrillation.

Setting

A Canadian community-based hospital.

Design

Medical records of patients who were diagnosed with acute onset atrial fibrillation at our hospital over a 2-year period were reviewed. Patients were included if intravenous amiodarone or intravenous procainamide was used for cardioversion.

Main Outcome Measures

Primary endpoints included conversion to and maintenance of normal sinus rhythm (NSR) and time to conversion. Secondary endpoints included duration and cost of treatment, and incidence of side effects.

Results

Sixteen patients met inclusion criteria: 9 received procainamide and 7 received amiodarone. Fifteen of the sixteen patients converted to and maintained NSR during their hospital stay. Conversion to NSR occurred in 33% and 0% of patients by 8 hours and in 56% and 29% of patients by 24 hours of treatment in the procainamide and amiodarone groups, respectively. The majority of patients (67%) in the amiodarone group converted to NSR after receiving greater than 24 hours of treatment. Conversion with amiodarone took 8 times longer than with procainamide. The median time to conversion was 5 hours for procainamide and 44 hours for amiodarone. The average cost of treatment was 20 times higher with amiodarone than procainamide. For patients in the amiodarone group, the average treatment cost was \$916.07 CAN, whereas with procainamide the average treatment cost was \$42.64 CAN. Hypotension was observed in 22% of patients, all in the procainamide group.

Conclusions

The results of this study suggest that both intravenous amiodarone and intravenous procainamide seem to be effective at converting acute onset atrial fibrillation. Intravenous procainamide appears to convert patients to NSR faster with few side effects and at a lower cost.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2001;4:404.

A study of the pharmacokinetic profile of low dose hepatitis B immune globulin (HBIG) in long-term liver transplant recipients for chronic hepatitis B infection

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Context

Post-transplant protocols for HBV prophylaxis using high dose intravenous HBIG (10,000 IU) $\pm$ lamivudine are commonly reported. Our centre has previously reported a low dose IM protocol and lamivudine with excellent results. There have been, however, no pharmacokinetic studies of IM HBIG in this setting.

Objectives

Our objective was to determine the pharmacokinetic profile of IM HBIG in long-term post-transplant recipients to determine a rational dosing protocol.

Setting

An outpatient liver transplant clinic at Vancouver General Hospital.

Design

Six patients receiving monthly HBIG IM injections (Nabiâ 1560 IU, n=3; Bay-Hepâ 2170 IU, n=3) for greater than one year were studied. HBIG titers (anti-HBs) were determined three times weekly for four weeks and then twice weekly. The pharmacokinetic parameters were calculated using non-compartment methods.

Main Outcome Measures

The outcome measures were pharmacokinetic parameters for IM HBIG injection in stable liver transplant recipients.

Results

The mean half-life of IM HBIG was approximately 10.5 days (range 4-20).

Conclusions

Based on these pharmacokinetic parameters in stable long-term post-transplant patients, a rational dosing protocol can be developed which allows for more appropriate utility of HBIG and improved patient convenience.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2001;4:405.

Impact of a cardiac discharge order form on the use of proven-effective therapies in post myocardial infarction patients

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 10, 2000. (Unfunded study).

Context

Despite clinical trial evidence and established treatment guidelines, there is current underusage of proven effective therapies in post acute myocardial infarction (AMI) patients.

Objectives

The purpose of this study was to assess the frequency and appropriateness of discharge drug therapy, and to assess the impact of a new cardiac discharge prescription order form on the use of proven effective therapies.

Setting

A 400 bed, acute care teaching institution.

Design

We conducted a retrospective chart review (from May 1, 1999 to July 31, 1999) to establish current discharge prescribing trends. After the implementation of the cardiac form, we conducted another chart review (from January 1, 2000 to March 31, 2000) to observe the impact of the form on the frequency and appropriateness of use of these therapies. Patient demographics and specific information regarding a patient's indication or contraindication for the following medication therapies were collected: ACE inhibitors, anticoagulants, antiplatelet drugs, beta-blockers, and lipid lowering agents.

Main Outcome Measures

The outcome measures were frequency and appropriateness of use of therapies for post acute myocardial infarction (AMI) patients.

Results

Pre-implementation period we reviewed 102 charts (92 evaluable) and post-implementation period reviewed 35 charts (33 evaluable). Observed a trend of stable or improved usage of proven effective therapies in eligible patients: ACE inhibitors 59% to 83%, anticoagulants 69% to 100%, antiplatelet drugs 98% to 100%, beta-blockers 97% to 94%, and lipid lowering agents 69% to 61%. When the cardiac form was used there was excellent use of proven effective therapies with 100% of eligible patients receiving the indicated therapy.

Conclusions

There was a trend towards an improved use of post AMI medications after implementation of a new cardiac discharge prescription form. When the new form is employed, use of proven effective therapies is optimized.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2000;4:406.

The effect and economic impact of standardized order forms on the prevention and treatment of post-operative nausea and vomiting (PONV) in hospitalized gynecological surgery patients

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 10, 2000. (Unfunded study).

Context

The risk of post-operative nausea and vomiting (PONV) following gynecological surgery remains high despite effective prophylactic medications.

Objectives

The objectives of this study were to determine if standardized orders for the prophylaxis and treatment of PONV in gynecological surgery patients: 1) reduce PONV occurrence; 2) reduce total costs; and 3) influence the choice of medications used for PONV prophylaxis and treatment.

Setting

A large Canadian tertiary care adult teaching hospital.

Design

A retrospective design was employed in which a random sample of 200 patients was selected from each of the two 6 month phases before (pre) and after (post) the implementation of standardized orders for PONV prophylaxis and treatment.

Main Outcome Measures

The primary outcome was the occurrence of any PONV episode. Logistic regression was used to adjust for potential confounding factors.

Results

Characteristics were similar except for surgical and anesthesia length between phases. The proportion of patients receiving PONV prophylaxis increased from 31% (pre) to 47% (post, $p=0.002$). There was a reduction in the risk of a PONV event in the post phase (OR= 0.67, 95% CI 0.67 – 0.97, $p=0.04$). The risk of PONV was significantly reduced with the administration of prophylactic medications (OR = 0.46, 95% CI 0.46 to 0.67). There was a reduction in the mean number of PONV episodes in the post phase (1.81 events) versus the pre phase (1.47 events, $p=0.02$). A reduction in mean PONV management costs was observed in the post phase (\$8.31, SD 8.50) as compared to the pre-phase (\$10.23, SD 8.25, $p=0.02$).

Conclusions

The implementation of pre-printed order forms for PONV prophylaxis and treatment appears to be an effective and economically attractive strategy.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2001;4:407

Comparison of two needle sizes for subcutaneous administration of enoxaparin: Effects on size of hematoma formation and pain on injection

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 10, 2000. (Supported by a grant from Rhone-Poulenc Rorer. This study was carried out solely under the direction of the authors.)

Context

Nursing staff at our institution have reported frequent, large hematomas at subcutaneous injection sites when administering enoxaparin. Reports from the literature and the manufacturer suggest hematomas develop at subcutaneous injection sites in 5.1 to 19.3% of patients. Use of a smaller needle size has been anecdotally reported to limit injection site hematomas when administering enoxaparin.

Objectives

To determine if using a 30-gauge, 5/16" insulin syringe versus a 26-gauge, 3/8" tuberculin syringe would significantly reduce the size of injection site hematomas and/or cause less pain on injection when patients were treated with enoxaparin (1mg/kg q12h) for unstable angina or non-Q-wave myocardial infarction.

Setting

The emergency department, intensive care unit, and cardiology ward of a 675-bed community hospital in Canada.

Design

A prospective, randomized study. Patients presenting to the emergency department with unstable angina or non-Q-wave myocardial infarction and prescribed enoxaparin were randomized to receive

subcutaneous injections by one of the two study needles. Every twelve hours, prior to the next administered dose, nurses inspected designated injection sites and measured any hematomas present. After the dose, nurses asked the patient to rate the pain on injection.

Main Outcome Measures

Size of largest hematoma formed, measured at the widest diameter in centimeters. Pain associated with injection, using a 10-point numerical pain scale.

Results

There was no significant difference in the median size of the largest hematoma (3.5 cm with the insulin syringe group versus 2.3 cm with the tuberculin syringe group, $p=0.68$) and no significant difference in the average pain score (0.31 units with the insulin syringe group versus 0.53 units with the tuberculin syringe group, $p=0.10$).

Conclusions

Use of a 30-gauge, 5/16" insulin syringe versus a 26-gauge, 3/8" tuberculin syringe does not significantly reduce hematoma size nor does it significantly reduce pain on injection.

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Pharmacotherapy on the Web

The Journal of Informed Pharmacotherapy 2001;4:500.

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Name of site:	HandHeldMed
Type of site:	Information site devoted to handheld computing applications in health care
Authoring organization:	HandHeldMed.com
Sponsors:	Supported through banner advertising and sales of software products.
Of particular interest to:	Any health professional who owns or is considering owning a handheld computer (eg. Palm Pilot, Visor, Pocket PC)
Completeness Score (/5)	4
Credibility Score (/5)	4
Usability Score (/5)	4
Why is it useful? (what will it help me DO?):	Provides a community for learning about how to maximize the capabilities of your handheld computer in your practice.
Commentary:	HandHeldMed's site is stocked with a wide variety of content ranging from numerous shareware and freeware products for the Palm computing platform (notably, Patient Tracker, an excellent monitoring tool) to columns, features, and product reviews. This site is one of the best places to keep track of trends in medical applications for handheld computing. One drawback is that it is fairly product-heavy, meaning that many areas of the site are aimed at promoting products the company sells itself.
URL of site:	http://www.handheldmed.com
Reviewed by:	Peter Loewen, Pharm.D.

Name of site:	Integrated Medical Curriculum
Type of site:	Multimedia medical reference & teaching site.
Authoring organization:	Gold Standard Multimedia
Sponsors:	Gold Standard Multimedia
Of particular interest to:	Any health professional who wishes to expand their knowledge of medicine.
Completeness Score (/5)	4
Credibility Score (/5)	5
Usability Score (/5)	5
Why is it useful? (what will it help me DO?):	Provides an appealing and interactive reference with multimedia illustrations to learn more about anatomy, physiology, histology, immunology, even medical ethics
Commentary:	Although the JIP has previously featured <u>Clinical Pharmacology 2000</u> in this section, the recent redesign of the Integrated Medical Curriculum section of Gold Standard Multimedia's site warrants its own review. Although not aimed specifically at pharmacotherapy practitioners, this site has much to offer practitioners and students who want to learn more about, say, physical assessment or physiologic systems and how they relate to pharmacotherapy. The Quicktime videos provided for many descriptions are exactly what the internet was designed to do: break the textbook mold and provide more valuable learning experiences. Best of all, all the content is FREE.
URL of site:	http://imc.gsm.com/
Reviewed by:	Peter Loewen, Pharm.D.

Name of site:	UBC Centre for Health Services and Policy Research
Type of site:	Information site collating several recent articles about the influence of the pharmaceutical industry on medical practice.
Authoring organization:	University of British Columbia Centre for Health Services and Policy Research
Sponsors:	None
Of particular interest to:	Pharmacotherapy practitioners and physicians interested in the pharmaceutical industry's influences on health care.
Completeness Score (/5)	2 (not intended to be a comprehensive site)
Credibility Score (/5)	5
Usability Score (/5)	4
Why is it useful? (what will it help me DO?):	Nothing in particular, except read some interesting articles and listen to some interesting interviews about the negative effects of the pharmaceutical industry.
Commentary:	This site is highlighted because it currently features a collection of articles and radio interviews drawn from a number of sources in the mass media.

URL of site:	http://www.chspr.ubc.ca/
Reviewed by:	Peter Loewen, Pharm.D.

Name of site:	Center For Evidence-Based Medicine

Type of site:	Information and teaching resources for EBM

Authoring organization:	UK's National Health Service

Sponsors:	NHS

Of particular interest to:	Pharmacotherapy and medical practitioners interested in honing their critical appraisal and clinical skills.

Completeness Score (/5)	5

Credibility Score (/5)	5

Usability Score (/5)	3

Why is it useful? (what will it help me DO?):	Provides a myriad of tools and information designed to help practitioners increase the degree to which they find, interpret and apply evidence in their clinical practice.

Commentary:	Calculating SpPins and SnNouts, likelihood ratios, NNT's and NNH's is easy with the spreadsheets and calculators available in the EBM Toolbox. The Teaching Materials section provides curricula for teaching others (and yourself) about how to "do" EBM. The collection of 63 "CATs", or Critical Appraised Topics, in the CATbank are a quick way to answer common clinical questions.

URL of site:	http://cebm.jr2.ox.ac.uk/

Reviewed by:	Peter Loewen, Pharm.D.

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Journal of Informed Pharmacotherapy 2001;5 (April-June)

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- Pharmacokinetics of cefuroxime axetil oral suspension in elderly volunteers
Christopher Wood, Mark Ling, Vanessa Herring, Scott Hanes, Bradley Boucher

Evidence-Based Reviews of the Pharmacotherapeutic Literature with emphasis on interpretation of the findings, designed to help practitioners put the findings into proper perspective

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Updated
April 15, 2002

Editorial

The Journal - One Year Later, and the Changing Culture of Academic Publishing

How time flies! Just 12 months ago, the first issue of The Journal of Informed Pharmacotherapy (or the "JIP") was launched. Our vision of a peer-reviewed online journal devoted to the practice of rational pharmacotherapy through the use of evidence-based principles came to fruition on April 1, 2000 and since then, the journal has grown beyond our expectations and continues to expand in both our readership and contributors. Today the JIP has over 12,000 visits to the website each month and this number continues to grow. The JIP fosters the rapid widespread dissemination of original research findings, as well as information intended to help pharmacotherapy practitioners provide better care for their patients. One year later, the JIP continues to be the only peer-reviewed online journal devoted to pharmacotherapy which does not require a paid subscription to access.

The Journal maintains five major sections which include Original Research, Issues in Pharmacotherapy Practice, Evidence-Based Pharmacotherapy Reviews, Research Abstracts and Pharmacotherapy on the Web. The JIP has now published 5 issues containing 2 Original Research articles, 10 Issues in Pharmacotherapy Practice papers, 26 Evidence-Based Pharmacotherapy Reviews, 23 Research Abstracts and 29 Pharmacotherapy on the Web reviews and our acceptance rate for peer-reviewed manuscripts is 75%. Over the past year, we've been able to expand our services by making the Mobile Edition of the JIP available to handheld computer users via AvantGo.

On a larger scale, changes in the field of academic publishing have continued to accelerate over the past 12 months. Since we launched the JIP, numerous electronic journals in other medical specialties have arisen and continue to shape the landscape of alternative academic publishing. One index of online journals, FreeMedicalJournals.com currently lists more than 600 journals which are available "free online". Although this site did not provide statistics concerning the growth in the number of journals it lists, the number of people accessing the site as a portal to online journals grew from 57,000 in July 2000 to 221,000 per month in March 2001, (1) signaling the continued rapid rise in use of the internet as a source for research findings.

Although the number of journals which are "online" continues to grow rapidly, a quick review of the most popular medical journals reveals that the transition to making their full content available to all users for free is far from complete, and possibly even in reverse. The typical strategy among publishers is to entice readers with a period of free full-text online, then to limit access to paying customers after a few months. Annals of Internal Medicine closed free access to its journal last week. The American Society of Health-System Pharmacists has recently done the same, and the Annals of Pharmacotherapy is soon to follow. Moving to the web is a necessary step for these journals, but limiting access to their full content does little to address the needs of clinicians and researchers who require the information, and does nothing to assist librarians who are faced with double-digit journal cost increases despite general inflation rates of around 3%. These cost increases are even more disturbing when one considers

the significant cost savings associated with online (vs. print-based) publication and distribution.

It is difficult to imagine how this strategy is sustainable given the vociferous demands from researchers, clinicians, and information managers (e.g. librarians) for faster access to information at lower costs. The Association of Research Libraries reports that North American libraries spend 170% more on subscription costs than they did 15 years ago, yet buy 6% fewer titles than they did then despite an explosion in the number of journals available. (2) Monopolization of the scientific publishing outlets through mergers of mega-publishers are likely to continue to erode the ability of libraries to provide access to information. For example, Reed-Elsevier recently acquired 70 smaller journals in an 18-month period and the top two scientific/technical publishing houses (Reed-Elsevier and Wolters Kluwer) owned 2,300 journals in 1999. (3)

Our academic culture creates incentives for publishing in prestigious journals without regard to the cost to the research community of doing so. Much has been written elsewhere about where this mindset may lead us. (4,5)

The debate over academic publishing has not subsided in the past year, but has certainly become more enlightened now that courageous people have launched innovative and vibrant alternatives to for-profit and limited-access online journals. The Editors of the JIP applaud the efforts of such groups as BiomedCentral, The Lancet's Electronic Research Archive and PubMedCentral (formerly eBiomed) who seek to revolutionize the publication and distribution process by testing alternative methods of peer review and information delivery to researchers and clinicians. This is a process which invites the participation of all clinicians and researchers, not just the privileged few on the editorial boards of specific journals. We also congratulate journals such as The Lancet (owned by Reed-Elsevier), the British Medical Journal, the Canadian Medical Association Journal and others who, despite being part of the traditional print media world, continue to offer free full-text access to their journals online. Finally, the rise of small independent online-only journals (e.g. Online Journal of Cardiology, Internet Journal of Emergency and Intensive Care Medicine, and others) is heartening and we believe that the efforts of these journals will help to shape the future of how we access and use medical information.

In time, the best strategies for compilation and delivery of online clinical data will emerge and flourish. In the meantime, all the avenues currently being explored, including the approach taken by the JIP, will teach us the right and wrong ways to proceed.

The contention among traditionalists that the quality of information will suffer as a result of alternative methods of peer-review and earlier access to research findings will be judged by its consumers... consumers who are unlikely to accept a return to more limited access and higher acquisition costs regardless of the outcome.

How for-profit and society-supported journals design their revenue models is up to them. As for the JIP, we will continue, along with many other publishers, to provide a no-cost wide access alternative to the for-profit limited access means of sharing information others in the pharmacotherapy field have chosen.

As our first editorial one year ago stated, ultimately the value of the JIP will be determined by its

authors and its readers. (6) To the authors and Editorial Board members who have contributed to the JIP, we thank you. To our readers, we continue to appreciate your positive and negative feedback.

Peter S. Loewen, B.Sc.(Pharm), Pharm.D.

Peter J. Zed, B.Sc.(Pharm), Pharm.D.

J Inform Pharmacother 2001;5:1.

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Original Research Article

Pharmacokinetics of Cefuroxime Axetil Oral Suspension in Elderly Volunteers

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Abstract

Objective: To determine the pharmacokinetics of cefuroxime (CXM) oral suspension in healthy, elderly volunteers.

Methods: A single 250 mg dose of CXM oral suspension (250 mg/5 ml) was administered to twelve healthy, elderly volunteers. Serum samples for CXM analysis were collected at baseline (pre-dose), 15, 30, 60, 90 and 120 minutes, and 3, 4, 6, 8, 10, and 12 hours after the dose. Serum CXM concentrations were analyzed using high-performance liquid chromatography. Pharmacokinetic (PK) parameters were determined using noncompartmental analysis.

Results: Twelve subjects (9 male, 3 female) completed the study. Demographic results were as follows (means $\pm$ standard deviations): age, 71 ± 3.7 years; weight, 77 ± 13 kg; estimated Cl_{Cr} , 67 ± 13 ml/min. Composite PK parameters were as follows (means $\pm$ standard deviations): C_{max} , 3.38 ± 0.77 mg/ml; $t_{1/2}$, 1.9 ± 0.2 hr; k_{el} , 0.36 ± 0.04 hr⁻¹; CL/F, 0.22 ± 0.05 ml/min/kg; AUC_{0-4} , 15.7 ± 2.6 mg*hr/ml; V/F, 0.59 ± 0.12 l/kg. Median T_{max} was 3 hours (interquartile range 2 - 4 hours). Previously published PK studies of a 250 mg dose of CXM oral suspension in younger volunteers (19-40 years) reported similar C_{max} and T_{max} values; however, $t_{1/2}$ was 0.5 - 0.7 hours. longer and AUC_{0-4} was 10 - 58% higher in the current study.

Conclusions: Cefuroxime axetil oral suspension in elderly subjects produces similar C_{max} and T_{max} values compared to previous data in younger subjects. The suspension appears to be an acceptable alternative to CXM tablets in the elderly.

J Inform Pharmacother 2001;5:100-103.

Introduction

Cefuroxime axetil (CXM) is a second-generation cephalosporin antibiotic with activity against a variety of Gram-positive and Gram-negative organisms. It is effective for the treatment of upper and lower respiratory tract, urinary tract, and skin and soft tissue infections (1). CXM is available as a film-coated tablet and an oral suspension formulation intended for use in children ages 3 months and older. However, elderly patients may also benefit from a liquid dosage form because factors such as impaired cognition, presence of feeding tubes, dysphagia, and dysmotility may make the administration of tablets difficult or dangerous. To date, no data have been published describing the pharmacokinetics of CXM suspension in elderly volunteers. Determining the pharmacokinetics of CXM suspension in this population is important because it may generate lower peak serum concentrations than tablets (2,3). Additionally, elderly patients may have altered CXM pharmacokinetics due to age-related decreases in renal function (4). The purpose of this study was to determine the pharmacokinetics of CXM oral suspension in healthy, elderly volunteers.

Methods

The study was approved by the Western Institutional Review Board and written, informed consent was obtained for all subjects. Inclusion criteria were age > 60 years and ability to give informed consent. Exclusion criteria were history of allergy to penicillin or cephalosporin

antibiotics, acute or chronic illness that might alter the pharmacokinetics of CXM (e.g. renal insufficiency, congestive heart failure, gastroparesis), anemia, poor venous access, or treatment with other antimicrobial agents. Prior to beginning the protocol, a medical history, physical examination, and laboratory testing were performed including a complete blood count, comprehensive metabolic panel, and urinalysis.

Each patient received a single 250 mg dose of CXM oral suspension (Ceftin, GlaxoWellcome Inc., Research Triangle Park, NC.) immediately after eating breakfast in order to promote maximal drug absorption (1). Blood samples were collected at baseline (pre-dose), 15, 30, 60, 90 and 120 minutes, and 3, 4, 6, 8, 10, and 12 hours after the dose. Vital signs were monitored at baseline, 30 and 60 minutes, and 3, 6, and 12 hours after the dose. After blood collection was completed, each patient returned for a follow up study visit within three days for a physical exam and to report adverse drug events.

Blood samples were centrifuged upon collection and the serum stored at -70°C until assayed. Serum samples were analyzed for cefuroxime by high-performance liquid chromatography using a modified version of an assay by Hanes et al. (5). Important assay modifications included monitoring absorbance at 280 nm instead of 255nm and removing the ion-pairing agent from the mobile phase. The CXM retention time was approximately 17.5 minutes. The assay was validated according to consensus guidelines (6). Extraction efficiency averaged 96% with less than 5% coefficient of variation across the concentration range for standards (0.1 µg/ml, 1 µg/ml, and 10 µg/ml). Within-day and between-day coefficients of variation for control concentrations (0.2 µg/ml, 2 µg/ml, and 7 µg/ml) were less than 5%. Assay results were considered valid only if the accuracy of standard and control concentrations was ± 10% of the known values for that day. The r² values for standard curves were greater than 0.98 for each day. Cefuroxime concentrations were determined using weighted linear regression (1/concentration²) from a line of best fit to the standard curve for that day.

Pharmacokinetic parameters were calculated from the CXM serum concentrations using noncompartmental analysis (7-9). The maximum serum concentration (C_{max}) and the time to reach this concentration (T_{max}) were visually determined directly from the concentration-time curves. The elimination constant (k_{el}) was determined by linear regression of the natural log of concentrations in the elimination phase (8). Terminal concentrations that were in a straight line based on visual inspection of a log-linear data plot were used to calculate k_{el} (8). The t_{1/2} was determined by 0.693/k_{el}. The area under the curve from time 0 to the last concentration (AUC₀₋₁₂) was determined using the linear trapezoidal rule. The area under the curve from time 0 to infinity (AUC_{0-∞}) was extrapolated by dividing the last measured concentration by the k_{el} and adding this value to the AUC₀₋₁₂ (9). Oral clearance (CL/F) was determined by dose/AUC_{0-∞}. Oral volume of distribution (V/F) was determined by dose/(AUC_{0-∞}* k_{el}). Creatinine clearance was estimated using the Cockcroft-Gault equation (10).

Results

Twelve subjects were enrolled in the study and no adverse drug effects were reported. Patient characteristics and pharmacokinetic results are shown the Table I. A composite concentration-time curve for all study subjects is depicted in the Figure 1. Extrapolated AUC_{12-∞} accounted for only 2 – 6% (mean 3%) of AUC_{0-∞}.

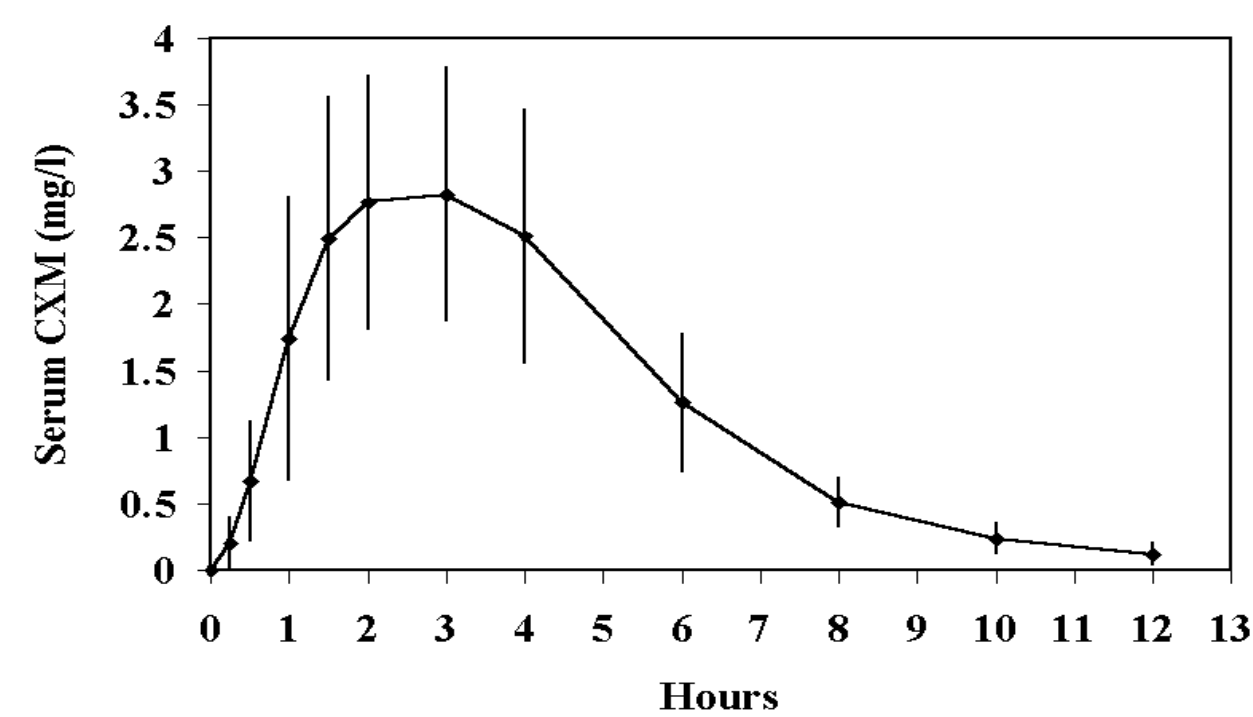
Table I. Patient Characteristics and Pharmacokinetic Parameters

Patient	Gender	Age (yrs)	Height (cm)	Weight (kg)	Est Cl _{Cr} (ml/min)	C _{max} (mg/l)	T _{max} (h)	k _{el} (h ⁻¹)	t _{1/2} (h)	AUC ₀₋₄ (µg•h/ml)	CL/F (l/h/kg)	V/F (l/kg)
1	M	74	175	77	54	2.38	6	0.320	2.2	17.5	0.19	0.58
2	M	73	179	86	80	3.81	4	0.348	2.0	14.1	0.21	0.59
3	F	70	152	60	62	2.71	4	0.451	1.5	14.4	0.29	0.64
4	M	69	155	86	85	2.35	3	0.322	2.2	11.3	0.26	0.80
5	M	70	187	87	65	3.45	2	0.349	2.0	15.7	0.18	0.53
6	M	73	178	95	80	3.27	1.5	0.369	1.9	12.6	0.21	0.56
7	F	73	150	60	48	3.47	2	0.398	1.7	13.7	0.30	0.76
8	M	68	168	75	75	2.48	6	0.354	2.0	16.5	0.20	0.57

9	F	63	160	50	46	3.52	4	0.381	1.8	18.6	0.27	0.70
10	M	77	175	85	62	4.21	3	0.308	2.3	19.1	0.15	0.50
11	M	68	183	85	77	4.36	1.5	0.429	1.6	17.0	0.17	0.40
12	M	73	173	81	75	4.54	3	0.335	2.1	19.1	0.16	0.48
Mean ± SD		71 ± 4	170 ± 12	77 ± 14	67 ± 13	3.38 ± 0.77		0.360 ± 0.04	1.9 ± 0.2	15.8 ± 2.6	0.22 ± 0.05	0.59 ± 0.12
Median (25-75%)							3 (2-4)					

CL_{Cr} = creatinine clearance, C_{max} = maximum concentration, T_{max} = time to maximum concentration, k_{el} = elimination constant, t_{1/2} = half-life, AUC₀₋₄ = area under the curve from time zero to infinity, CL/F = oral clearance, V/F = oral volume of distribution

Figure 1: Composite Concentration-Time Curve for all Subjects.



The concentration-time curve represents the mean CXM concentration (± one standard deviation) at each time point sampled.

Discussion

In this study, mean CXM C_{max} and median T_{max} values were similar to those previously reported in younger adult volunteers (19-40 years) following a single 250 mg dose of CXM oral suspension (ranges: 2.48 - 3.85 mg/l and 2.0 - 3.6 h) (2,3,11). These results indicate good bioavailability of CXM oral suspension in elderly subjects; however, two subjects had a delayed T_{max} of six hours. The reason for apparent delayed absorption in these subjects is unknown. Mean t_{1/2} and AUC₀₋₄ were mildly increased compared to previous data in younger volunteers (ranges: 1.2 - 1.4 h and 10 - 14.4 mg•h/l) (2,3,11). The modest elevations in t_{1/2} and AUC₀₋₄ observed are likely due to age-related decreases in renal function and would not be expected to result in clinically significant accumulation with Q12 hour dosing. Cefuroxime has a good safety profile even with high dose intravenous therapy that produces much higher serum concentrations than those observed in this study (12). A more sophisticated multiple-dose study would be needed to provide definitive dosing guidelines; however, the results of this study suggest that no dose adjustment is needed in elderly subjects with normal renal function. Currently, dosing changes for impaired renal function are not recommended until CL_{Cr} is less than 30 ml/min (1).

The major limitation of this study is that there was not a control group of elderly volunteers who received CXM tablets. A previous study of

CXM tablets (250 mg Q12H) in elderly patients has been published and showed a higher $C_{\max}$ and longer $t_{1/2}$ than our study (13). However, comparisons with the current data are difficult. The higher $C_{\max}$ in the previous study may have been due to a lower mean body weight seen in the former study (57 vs. 77 kg), and the longer $t_{1/2}$ may have been because of poorer renal function (mean estimated CL_{Cr} 35 vs. 67 ml/min) (13). Nonetheless, the present data show that CXM oral suspension in elderly volunteers results in similar $C_{\max}$ and $T_{\max}$ values to those previously reported in younger volunteers. Cefuroxime axetil oral suspension appears to be an acceptable alternative to CXM tablets in elderly patients.

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Pharmacokinetics of Cefuroxime Axetil Oral Suspension in Elderly Volunteers

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Objective: To determine the pharmacokinetics of cefuroxime (CXM) oral suspension in healthy, elderly volunteers.

Methods: A single 250 mg dose of CXM oral suspension (250 mg /5 ml) was administered to twelve healthy, elderly volunteers. Serum samples for CXM analysis were collected at baseline (pre-dose), 15, 30, 60, 90 and 120 minutes, and 3, 4, 6, 8, 10, and 12 hours after the dose. Serum CXM concentrations were analyzed using high-performance liquid chromatography. Pharmacokinetic (PK) parameters were determined using noncompartmental analysis.

Results: Twelve subjects (9 male, 3 female) completed the study. Demographic results were as follows (means $\pm$ standard deviations): age, 71 ± 3.7 years; weight, 77 ± 13 kg; estimated Cl_{Cr} 67 ± 13 ml/min. Composite PK parameters were as follows (means $\pm$ standard deviations): C_{max} , 3.38 ± 0.77 μ g/ml; $t_{1/2}$, 1.9 ± 0.2 hr; k_{el} , 0.36 ± 0.04 hr⁻¹; CL/F , 0.22 ± 0.05 ml/min/kg; AUC_{0-4} , 15.7 ± 2.6 μ g*hr/ml; V/F , 0.59 ± 0.12 l/kg. Median T_{max} was 3 hours (interquartile range 2 - 4 hours). Previously published PK studies of a 250 mg dose of CXM oral suspension in younger volunteers (19-40 years) reported similar C_{max} and T_{max} values; however, $t_{1/2}$ was 0.5 - 0.7 hours. longer and AUC_{0-4} was 10 - 58% higher in the current study.

Conclusions: Cefuroxime axetil oral suspension in elderly subjects produces similar C_{max} and T_{max} values compared to previous data in younger subjects. The suspension appears to be an acceptable alternative to CXM tablets in the elderly.

J Inform Pharmacother 2001;5:100-103.

Cefuroxime axetil (CXM) is a second-generation cephalosporin antibiotic with activity against a variety of Gram-positive and Gram-negative organisms. It is effective for the treatment of upper and lower respiratory tract, urinary tract, and skin and soft tissue infections (1). CXM is available as a film-coated tablet and an oral suspension formulation intended for use in children ages 3 months and older. However, elderly patients may also benefit from a liquid dosage form because factors such as impaired cognition, presence of feeding tubes, dysphagia, and dysmotility may make the administration of tablets difficult or dangerous. To date, no data have been published describing the pharmacokinetics of CXM suspension in elderly volunteers. Determining the pharmacokinetics of CXM suspension in this population is important because it may generate lower peak serum concentrations than tablets (2,3). Additionally, elderly patients may have altered CXM pharmacokinetics due to age-related decreases in renal function (4). The purpose of this study was to determine the pharmacokinetics of CXM oral suspension in healthy, elderly volunteers.

Methods

The study was approved by the Western Institutional Review Board and written, informed consent was obtained for all subjects. Inclusion criteria were age > 60 years and ability to give informed consent. Exclusion criteria were history of allergy to penicillin or cephalosporin antibiotics, acute or chronic illness that might alter the pharmacokinetics of CXM (e.g. renal insufficiency, congestive heart failure, gastroparesis), anemia, poor venous access, or treatment with other antimicrobial agents. Prior to beginning the protocol, a medical history, physical examination, and laboratory testing

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were performed including a complete blood count, comprehensive metabolic panel, and urinalysis.

Each patient received a single 250 mg dose of CXM oral suspension (Ceftin, GlaxoWellcome Inc., Research Triangle Park, NC.) immediately after eating breakfast in order to promote maximal drug absorption (1). Blood samples were collected at baseline (pre-dose), 15, 30, 60, 90 and 120 minutes, and 3, 4, 6, 8, 10, and 12 hours after the dose. Vital signs were monitored at baseline, 30 and 60 minutes, and 3, 6, and 12 hours after the dose. After blood collection was completed, each patient returned for a follow up study visit within three days for a physical exam and to report adverse drug events.

Blood samples were centrifuged upon collection and the serum stored at -70°C until assayed. Serum samples were analyzed for cefuroxime by high-performance liquid chromatography using a modified version of an assay by Hanes et al. (5). Important assay modifications included monitoring absorbance at 280 nm instead of 255nm and removing the ion-pairing agent from the mobile phase. The CXM retention time was approximately 17.5 minutes. The assay was validated according to consensus guidelines (6). Extraction efficiency averaged 96% with less than 5% coefficient of variation across the concentration range for standards (0.1 µg/ml, 1 µg/ml, and 10 µg/ml). Within-day and between-day coefficients of variation for control concentrations (0.2 µg/ml, 2 µg/ml, and 7 µg/ml) were less than 5%. Assay results were considered valid only if the accuracy of standard and control concentrations was $\pm 10\%$ of the known values for that day. The r^2 values for standard curves were greater than 0.98 for each day. Cefuroxime concentrations were determined using weighted linear regression ($1/\text{concentration}^2$) from a line of best fit to the standard curve for that day.

Pharmacokinetic parameters were calculated from the CXM serum concentrations using noncompartmental analysis (7-9). The maximum serum concentration ($C_{\max}$) and the time to reach this concentration ($T_{\max}$) were visually determined directly from the concentration-time curves. The elimination constant (k_{el}) was determined by linear regression of the natural log of concentrations in the elimination phase (8). Terminal concentrations that were in a straight line based on visual inspection of a log-linear data plot were used to calculate k_{el} (8). The $t_{1/2}$ was

determined by $0.693/k_{\text{el}}$. The area under the curve from time 0 to the last concentration (AUC_{0-12}) was determined using the linear trapezoidal rule. The area under the curve from time 0 to infinity (AUC_{0-4}) was extrapolated by dividing the last measured concentration by the k_{el} and adding this value to the AUC_{0-12} (9). Oral clearance (CL/F) was determined by $\text{dose}/\text{AUC}_{0-4}$. Oral volume of distribution (V/F) was determined by $\text{dose}/(\text{AUC}_{0-4} * k_{\text{el}})$. Creatinine clearance was estimated using the Cockcroft-Gault equation (10).

Results

Twelve subjects were enrolled in the study and no adverse drug effects were reported. Patient characteristics and pharmacokinetic results are shown in Table I. A composite concentration-time curve for all study subjects is depicted in Figure 1. Extrapolated AUC_{12-4} accounted for only 2 - 6% (mean 3%) of AUC_{0-4} .

Discussion

In this study, mean CXM $C_{\max}$ and median $T_{\max}$ values were similar to those previously reported in younger adult volunteers (19-40 years) following a single 250 mg dose of CXM oral suspension (ranges: 2.48-3.85 mg/l and 2.0-3.6 h) (2,3,11). These results indicate good bioavailability of CXM oral suspension in elderly subjects; however, two subjects had a delayed $T_{\max}$ of six hours. The reason for apparent delayed absorption in these subjects is unknown. Mean $t_{1/2}$ and AUC_{0-4} were mildly increased compared to previous data in younger volunteers (ranges: 1.2-1.4 h and 10-14.4 mg•h/l) (2,3,11). The modest elevations in $t_{1/2}$ and AUC_{0-4} observed are likely due to age-related decreases in renal function and would not be expected to result in clinically significant accumulation with Q12 hour dosing. Cefuroxime has a good safety profile even with high dose intravenous therapy that produces much higher serum concentrations than those observed in this study (12). A more sophisticated multiple-dose study would be needed to provide definitive dosing guidelines; however, the results of this study suggest that no dose adjustment is needed in elderly subjects with normal renal function. Currently, dosing changes for impaired renal function are not recommended until CL_{Cr} is less than 30 ml/min (1).

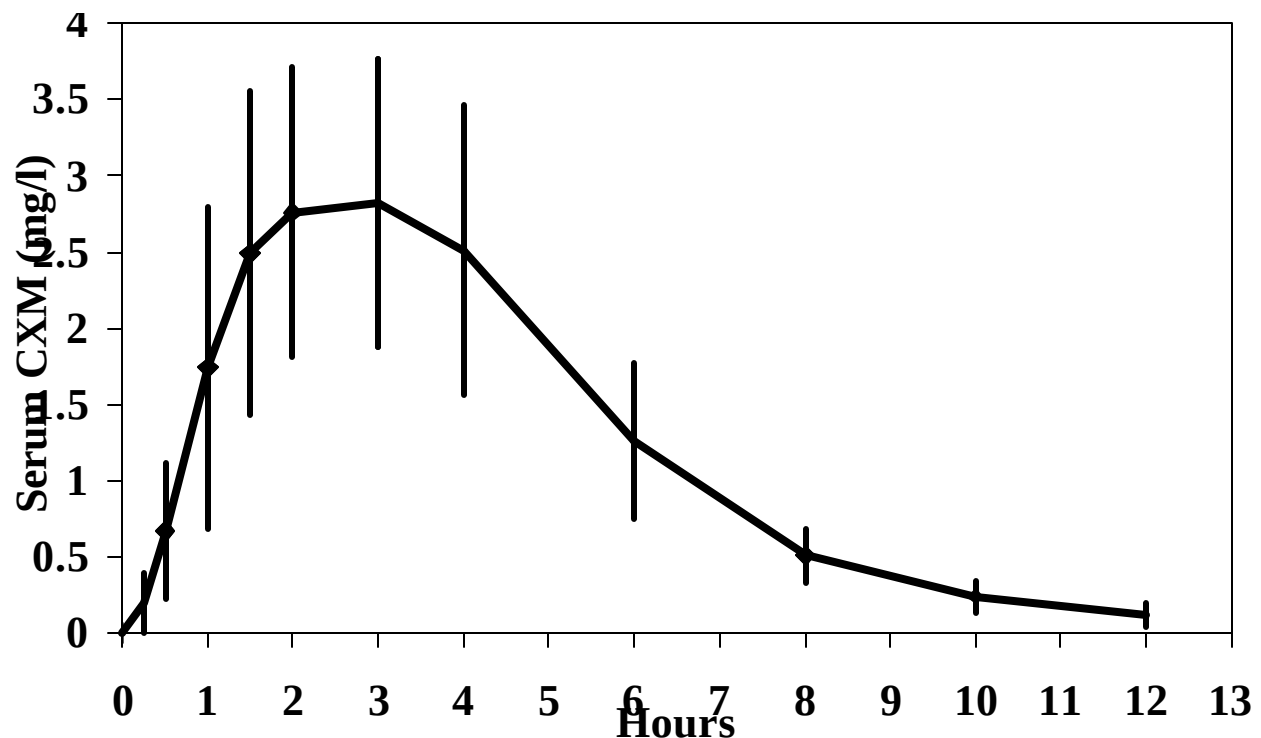
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Table I. Patient Characteristics and Pharmacokinetic Parameters

Patient	Gender	Age (yr)	Ht (cm)	Wt (kg)	Est Cl _{cr} (ml/min)	C _{max} (mg/l)	T _{max} (h)	k _{el} (h ⁻¹)	t _{1/2} (h)	AUC ₀₋₄ (mg*h/ml)	CL/F (l/h/kg)	V/F (l/kg)
1	M	74	175	77	54	2.38	6	0.320	2.2	17.5	0.19	0.58
2	M	73	179	86	80	3.81	4	0.348	2.0	14.1	0.21	0.59
3	F	70	152	60	62	2.71	4	0.451	1.5	14.4	0.29	0.64
4	M	69	155	86	85	2.35	3	0.322	2.2	11.3	0.26	0.80
5	M	70	187	87	65	3.45	2	0.349	2.0	15.7	0.18	0.53
6	M	73	178	95	80	3.27	1.5	0.369	1.9	12.6	0.21	0.56
7	F	73	150	60	48	3.47	2	0.398	1.7	13.7	0.30	0.76
8	M	68	168	75	75	2.48	6	0.354	2.0	16.5	0.20	0.57
9	F	63	160	50	46	3.52	4	0.381	1.8	18.6	0.27	0.70
10	M	77	175	85	62	4.21	3	0.308	2.3	19.1	0.15	0.50
11	M	68	183	85	77	4.36	1.5	0.429	1.6	17.0	0.17	0.40
12	M	73	173	81	75	4.54	3	0.335	2.1	19.1	0.16	0.48
Mean ± SD		71 ± 4	170 ± 12	77 ± 14	67 ± 13	3.38 ± 0.77		0.360 ± 0.04	1.9 ± 0.2	15.8 ± 2.6	0.22 ± 0.05	0.59 ± 0.12
Median (25-75%)							3 (2-4)					

CL_{cr} = creatinine clearance, C_{max} = maximum concentration, T_{max} = time to maximum concentration, k_{el} = elimination constant, t_{1/2} = half-life, AUC₀₋₄ = area under the curve from time zero to infinity, CL/F = oral clearance, V/F = oral volume of distribution

Figure 1: Composite Concentration-Time Curve for all Subjects.



The concentration-time curve represents the mean CXM concentration ($\pm$ one standard deviation) at each time point sampled.

The major limitation of this study is that there was not a control group of elderly volunteers who received CXM tablets. A previous study of CXM tablets (250 mg Q12H) in elderly patients has been published and showed a higher $C_{\max}$ and longer $t_{1/2}$ than our study (13). However, comparisons with the current data are difficult. The higher $C_{\max}$ in the previous study may have been due to a lower mean body weight seen in the former study (57 vs. 77 kg), and the longer $t_{1/2}$ may have been because of poorer renal function (mean estimated CL_{Cr} 35 vs. 67 ml/min) (13). Nonetheless, the present data show that CXM oral suspension in elderly volunteers results in similar $C_{\max}$ and $T_{\max}$ values to those previously reported in younger volunteers. Cefuroxime axetil oral suspension appears to be an acceptable alternative to CXM tablets in elderly patients.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;5:200-202.

Early Switch and Early Discharge Strategies for Community-Acquired Pneumonia: Can we Reduce Costs and Still Achieve the Desired Outcomes?

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Original Citation

Rhew DC, Tu GS, Ofman J, Henning JM, Richards MS, Weingarten SR. Early Switch and Early Discharge Strategies in Patients With Community-Acquired Pneumonia: A Meta-analysis. Arch Intern Med 2001 Mar 12;161:722-727. [PubMed Cit](#)

Overall Study Question

To evaluate criteria used in studies of community-acquired pneumonia (CAP) for early switch therapy (i. e. parenteral to oral therapy conversion) and to assess the impact of early switch and early discharge on clinical outcomes and length of stay (LOS). Several past studies have been published have suggested that early switch and early discharge may decrease the length of stay without adverse affecting outcomes.

Are the Results of the Study Valid?

1. Did the overview address a focused clinical question?

Yes. The authors specifically focused on the impact of early switch therapy and discharge on clinical outcomes and LOS.

2. Were the criteria used to select articles for inclusion appropriate?

Yes. The researchers searched several databases using several search terms for articles addressing early switch therapy antibiotic therapy and early discharge in CAP patients. Early switch and early discharge strategy was defined as a method or intervention designed to shorten LOS through early switch and/or early discharge recommendations. Articles were excluded if following existed less rigorous study design, specific patient population (e.g. unrelated to CAP), non-bacterial cause of CAP, non-clinical evaluation, unrelated study objective and absence of early switch criteria.

3. Is it unlikely that important, relevant studies were missed?

No. The authors searched for English language articles published between January 1, 1980 and March 31, 2000. The researchers searched MEDLINE, HEALTHSTAR, EMBASE, Cochrane Collaboration and Best Evidence databases for prospective and retrospective trials, meta-analyses and systematic reviews. The extent of search terms used would have captured the majority of relevant articles pertaining to the study question.

4. Was the validity of the included studies appraised?

The methodologies of articles selected were not evaluated specifically. The authors evaluated articles to address four areas of investigation; criteria for switch therapy, criteria for discharge, switch on specific day/length of parenteral therapy and outcomes.

5. Were assessments of studies reproducible?

The authors applied criteria to reviewed articles to compare criteria for early switch and early discharge in CAP. Only articles that examined LOS are included in the outcomes evaluation. Chi-square and random effects meta-analysis was conducted on LOS for qualifying studies. Evaluation of clinical outcomes between intervention and control groups was not well described. Kappa values for agreement were calculated for the article reviewers.

6. Were the results similar from study to study?

Differences in the criteria and methodology used in early switch and early discharge studies assessed by the researchers resulted in variation in results with respect to the LOS and discharge. This also made it difficult for the researchers to assess the outcome resulting from the early switch and/or discharge. Although mean age among assessed studies appeared similar, the researchers suggested the patients included in the pooled analysis may not have been similar. Two of the assessed studies enrolled "low-risk" patients with stays shorter than the interventional guidelines. Other factors accounting for the variation in LOS included geographic variation and secular trends.

What are the Results?

1. What are the overall results of the review?

The authors identified 1794 articles, of which 266 abstracts were reviewed. Only 10 prospective, interventional CAP studies involved an evaluation of LOS. Criteria for switch were reported in 9 studies. The most common criteria for switch was afebrile (100%), improvement/resolution of signs and symptoms (89%) and able to take oral antibiotics (67%). Five studies applied criteria for early discharge criteria with care of comorbid condition the most common. There was disparity in other discharge criteria among the 5 studies.

The median recommended day of switch therapy was 3 days (range 2-10 days) in 3 studies. Five studies recommended switch therapy after a minimum number of parenteral days (3 days, range 2-10). Chi-square analysis revealed significant variability ($p < 0.001$) in the LOS amongst the studies. Of the 10 prospective studies, 6 applied early switch and discharge criteria to an intervention and control group. The remaining 4 studies involved no control groups or used historical controls. Among the 6 evaluable studies, the LOS was quite variable (range, 3.5 to 11 days). Meta-analysis was performed on 5 studies where standard deviation values for LOS were provided. The mean change in LOS between the intervention and control was not significantly reduced ($p = 0.05$) based on a random effects meta-analysis (-1.64 days; 95% confidence interval -3.30 to 0.02). Two studies had an interventional LOS equal or longer than the control. Exclusion of these studies increased the mean change of LOS between the intervention and control group to 3 days (-3.04 days; 95% confidence interval -4.90 to -1.19).

2. How precise were the results?

As above.

3. How much does allowance for uncertainty change the results? (i.e. Sensitivity analysis? Analysis of heterogeneity?)

Sensitivity analysis or analysis of heterogeneity was not done. Characteristics of the 5 prospective interventional studies that may have confounded LOS analysis were presented.

Will the results help me in caring for my patients?

1. Can the results be applied to my patient care?

Although criteria for switch therapy are generally similar, there are variations in the definitions used among some of the studies. As noted above, there is considerable variability in the criteria for early discharge and LOS due to study design. Overall, the comparison of criteria used for early switch therapy provides guidance to clinicians when evaluating a patient for oral antibiotic therapy. The authors correctly indicate that the baseline LOS affects the impact (change in LOS) as a result of early switch or discharge interventions and must thus be considered if institutions were to implement similar programs.

2. Were all clinically important outcomes considered?

Due to differences in the methodology of the studies assessed, clinical outcomes (e.g. complications or therapeutic failures, mortality, readmission, quality of life, etc...) among the 10 prospective, interventional studies were not pooled and adequately examined.

3. Are the benefits worth the harms and costs?

Intuitively, the application of early switch and discharge criteria should decrease the LOS of stay. Early switch criteria such as the resolution of fever, clinical improvement and ability to ingest oral antibiotics are reasonable when evaluating antibiotic therapy in patients with CAP. Early switch therapy in hospitalized patients may yield cost savings with respect to antimicrobial costs. The use of early switch and early discharge for CAP may decrease LOS without adversely affecting outcome. It should be noted that economic impact of early switch therapy and/or early discharge were not evaluated in this study.

Commentary

With the increasing armamentarium of antibiotics directed specifically against CAP, there is perhaps increasing confusion with respect to the therapeutic differences among and within antibiotic classes. Methodological differences in CAP studies with respect to discharge criteria, LOS and clinical outcomes make it difficult to assess the impact of a given agent or class. Several studies have clearly shown that many patients admitted to hospital with CAP at low risk of mortality may be treated adequately as an outpatient. To assist clinicians, prognostic scoring has been used to assess the risk of mortality among patients with CAP and thus reduce unnecessary hospital admissions. Recent Canadian data suggests that the LOS appear longer than studies conducted in the US. (1) Hence approaches to decrease the cost of CAP-related hospitalization (early switch) and/or decrease the LOS (early discharge) may be of benefit. The findings of the study above confirm what clinicians have been intuitively using as a guide to convert patients from parenteral to oral therapy (resolution of temperature, clinical improvement and ability to take oral antibiotics). However, the clinical and economic impact of decreasing the LOS in Canada as a result of early switch and discharge interventions require critical evaluation through further research.

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What were the Results?

1. Can the results be applied to my patient care?

Although criteria for switch therapy are generally similar, there are variations in the definitions used among some of the studies. As noted above, there is considerable variability in the criteria for early discharge and LOS due to study design. Overall, the comparison of criteria used for early switch therapy provides guidance to clinicians when evaluating a patient for oral antibiotic therapy. The authors correctly indicate that the baseline LOS affects the impact (change in LOS) as a result of early switch or discharge interventions and must thus be considered if institutions were to implement similar programs.

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Due to differences in the methodology of the studies assessed, clinical outcomes (e.g. complications or therapeutic failures, mortality, readmission, quality of life, etc.) among the 10 prospective, interventional studies were not pooled and adequately examined.

3. Are the benefits worth the harms and costs?

Intuitively, the application of early switch and discharge criteria should decrease the LOS of stay. Early switch criteria such as the resolution of fever, clinical improvement and ability to ingest oral antibiotics are reasonable when evaluating antibiotic therapy in patients with CAP. Early switch therapy in hospitalized patients may yield cost savings with respect to antimicrobial costs. The use of early switch and early discharge for CAP may decrease LOS without adversely affecting outcome. It should be noted that economic impact of early switch therapy and/or early discharge were not evaluated in this study.

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Commentary

With the increasing armamentarium of antibiotics directed specifically against CAP, there is perhaps increasing confusion with respect to the therapeutic differences among and within antibiotic classes. Methodological differences in CAP studies with respect to discharge criteria, LOS and clinical outcomes make it difficult to assess the impact of a given agent or class. Several studies have clearly shown that many patients admitted to hospital with CAP at low risk of mortality may be treated adequately as an outpatient. To assist clinicians, prognostic scoring has been used to assess the risk of mortality among patients with CAP and thus reduce unnecessary hospital admissions. Recent Canadian data suggests that the LOS appear longer than studies conducted in the US. (1) Hence approaches to decrease the cost of CAP-related hospitalization (early switch) and/or decrease the LOS (early discharge) may be of benefit. The findings of the study above confirm what clinicians have been intuitively using as a guide to convert patients from parenteral to oral therapy (resolution of temperature, clinical improvement and ability to take oral antibiotics). However, the clinical and economic impact of decreasing the LOS in Canada as a result of early switch and discharge interventions require critical evaluation through further research.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;5:203-206.

One-to-one versus Group Sessions to Improve Prescribing in Primary Care: Is a Twosome Better than a Herd Approach?

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Reviewer's profession/specialty: Academic detailing/research

Original Citation

Figueiras A, Sastre I, Tato F, Rodriguez C, Lado E, Caamano F, Gestal-Otero JJ. One-to-one versus group sessions to improve prescription in primary care: a pragmatic randomized controlled trial. Med Care 2001;39:158-67. [PubMed Cit](#)

Overall Study Question

The primary objective of the study was to evaluate the effectiveness of one-to-one education and group education of physicians with the intent of improving the prescribing of non-steroidal anti-inflammatory drugs (NSAIDs) in primary care. The secondary objectives were to assess the duration of the education effect on prescribing, and determine whether or not printed materials (i.e. a reminder) increases the overall effectiveness of the educational strategies.

The study population involved general and family practice physicians in Galicia, Spain (population 2.7 million). Physicians in the one-to-one education group received a 20-minute outreach visit from 1 of 2 doctoral level pharmacists. Those physicians receiving group education attended a 45-minute session conducted by the same pharmacists. All subjects in both groups were provided with copies of relevant articles. In addition, some physicians in each education group were provided with an additional reminder (brief glossy printed material). The educational message for both groups included the recommendation that ibuprofen, naproxen and diclofenac are considered non-steroidal anti-inflammatory drugs (NSAIDs) of first choice for the treatment of osteoarthritis with inflammation.

The effect of the educational interventions was assessed by calculating the rate of prescribed units of the recommended NSAIDs relative to the total NSAIDs prescribed on a monthly basis for 2 years (15 months pre-education and 9 months post-education). ASA was excluded as it is seldom used as an NSAID

in Spain.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. The Galicia region was divided into 15 spatial clusters which were then randomly allocated into 3 study groups: 1) one-to-one education; 2) group education and; 3) control group. Within the 5 clusters allocated to the one-to-one education group, 98 physicians were randomly selected. Within the 5 clusters allocated to group education, 92 physicians from 8 health centres were selected. The control group included all physicians (n=405) from the remaining 5 clusters. Physicians were randomized by geographic areas rather than as individual prescribers to avoid intergroup cross-contamination.

In addition, some physicians in each of the educational groups were selected to receive glossy printed materials (i.e. reminders) to determine if these materials would increase the effectiveness of the intervention. How the physicians were allocated to the reminder or no reminder strata is unclear. In the one-to-one educational group, this was done 'systematically' (by weekday) such that 82% received the reminder. Two of the 8 centres receiving group education were allocated to not receive the reminder, however, 11 physicians at one of these centres did receive the reminder when they requested it.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. Ninety-four of the 98 physicians selected for one-to-one education took part in this intervention. Of the 92 physicians selected for group education, only 59 attended the educational session. While no explanation is provided for the non-participation, the statistical analysis was done by intention-to-treat.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

No. Prior to the start of the study, physicians in the one-to-one education group received a letter from the university conducting the study describing the study's objectives, source of funding (a government agency) and that a doctoral level pharmacist would contact them to arrange a meeting. The coordinators at each of the health centres where the physicians received group education received a similar letter. Researchers were blind to which physician had written which prescription.

4. Were the groups similar at the start of the trial?

Unable to determine. Only general and family practice physicians were included in the study. No other demographic information is provided.

5. Aside from the experimental intervention, were the groups treated equally?

No. While the introduction letter was sent to all physicians in the one-to-one education group, it was only sent to the coordinator of the health centre where the group education was taking place. Therefore, it is uncertain if all of the physicians in both groups had the same information about the study prior to its start. In addition, one group of 11 physicians receiving group education who initially were allocated to the non-reminder group received the printed material when they requested it.

6. Overall, are the results of the study valid?

Partially. The study results are valid in demonstrating that one-to-one education is more effective than group education on modifying the prescribing practices of physicians. Unfortunately, the results assessing the impact of using a printed reminder to enhance the effectiveness of the educational interventions is not valid as the randomization process is unclear and the results are only reported for one of the 2 educational strategies.

What were the Results?

1. How large was the treatment effect?

During the 9 months of follow-up, the physicians who received one-to-one education increased their rate of prescribing of the recommended NSAIDs by 6.5% in comparison to the control group ($p < 0.001$). The physicians who received group education increased the prescribing of the recommended NSAIDs by 2.4% in comparison to the control group ($p < 0.05$). One-to-one education was more effective than group education even after adjusting for the intended sample versus the actual sample (6.5% vs. 3.7%, $p < 0.05$).

In the one-to-one education group, the researchers report that the physicians who received the reminder prescribed significantly more of the recommended NSAIDs than the physicians that did not receive the reminder although the relative changes are not reported. The effect of the reminder in the group receiving group education was not reported.

2. How precise was the estimate of the treatment effect?

Unknown. No information is provided.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Not applicable.

2. Were all clinically important outcomes considered?

NSAIDs were selected as the focus of the educational interventions because the investigators felt that promoting the use of NSAIDs with lower gastrointestinal risk (i.e. ibuprofen, naproxen, diclofenac) could reduce the incidence of gastric lesions. While the study demonstrates that the educational strategies did increase the prescribing of these NSAIDs, it would have been interesting to see if there was a reduction in NSAID-associated adverse events (e.g. ulcers, bleeding, perforation, hospitalizations).

3. Are the likely treatment benefits worth the potential harms and costs?

No information is provided on the cost of conducting the educational interventions.

Commentary

The results of this study support previous reports that demonstrate that one-to-one education is effective in altering prescribing practices and the effect is sustained for at least 9 months (i.e. the duration of follow-up in this study). The comparison of one-to-one education to group education provides new information demonstrating that although group education is also effective at changing prescribing practices, one-to-one education is comparatively more effective. Although the investigators report that a reminder was effective in enhancing one-to-one education, it is unclear as to how the physicians were assigned to the reminder versus no reminder strata. The imbalance between the strata suggests that it was not randomized. As well, no analysis was conducted on the effect of the reminder on physician who received group education presumably because those physicians allocated to receive no reminder did receive the reminder. Accordingly, we should not attempt to draw any conclusions from this study regarding the ability of a printed reminder to enhance the effectiveness of one-to-one or group education on modifying prescribing behaviour.

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Reviewer's profession/specialty: Academic detailing/research

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2. How precise was the estimate of the treatment effect?

Unknown. No information is provided.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Not applicable.

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NSAIDs were selected as the focus of the educational interventions because the investigators felt that promoting the use of NSAIDs with lower gastrointestinal risk (i.e. ibuprofen, naproxen, diclofenac) could reduce the incidence of gastric lesions. While the study demonstrates that the educational strategies did increase the prescribing of these NSAIDs, it would have been interesting to see if there was a reduction in NSAID-associated adverse events (e.g. ulcers, bleeding, perforation, hospitalizations).

3. Are the likely treatment benefits worth the potential harms and costs?

No information is provided on the cost of conducting the educational interventions.

Commentary

The results of this study support previous reports that demonstrate that one-to-one education is effective in altering prescribing practices and the effect is sustained for at least 9 months (i.e. the duration of follow-up in this study). The comparison of one-to-one education to group education provides new information demonstrating that although group education is also effective at changing prescribing practices, one-to-one education is comparatively more effective. Although the investigators report that a reminder was effective in enhancing one-to-one education, it is unclear as to how the physicians were assigned to the reminder versus no reminder strata. The imbalance between the strata suggests that it was not randomized. As well, no analysis was conducted on the effect of the reminder on physician who received group education presumably because those physicians allocated to receive no reminder did receive the reminder. Accordingly, we should not attempt to draw any conclusions from this study regarding the ability of a printed reminder to enhance the effectiveness of one-to-one or group education on modifying prescribing behaviour.

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2000;5:207-209.

Therapy for Helicobacter pylori in Patients with Nonulcer Dyspepsia: Eradicate or Not?

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Reviewer's profession/specialty: Dialysis/ Residency Coordinator

Original Citation

Laine L, Schoenfeld P, Fennerty MB. Therapy for Helicobacter pylori in Patients with Nonulcer Dyspepsia. A Meta-Analysis of Randomized, Controlled Trials. Ann Intern Med 2001;134:361-369.
[PubMed Cit](#)

Overall Study Question

Helicobacter pylori (*H. pylori*) infection is a common manifestation with a Canadian prevalence of 20-40% in the general population and ~50% in patients with nonulcer dyspepsia. (1) While the eradication of *H. pylori* is the standard of care in patients with peptic ulcer disease (2), the role of this organism in nonulcer dyspepsia is controversial. (1,2) The purpose of this meta-analysis was to determine whether treatment of *H. pylori* infection in patients with nonulcer dyspepsia significantly improves symptoms. A secondary outcome was to determine whether patients whose *H. pylori* infection was cured had significantly less dyspepsia compared to those with persistent infection.

Are the Results of the Study Valid?

1. Did the overview address a focused clinical question?

Yes.

2. Were the criteria used to select articles for inclusion appropriate?

Yes. Criteria for study selection were defined a priori and included studies that: 1) involved patients with non-ulcer dyspepsia and documented *H. pylori* infections; 2) compared dual, triple or quadruple therapy for *H. pylori* with a placebo control; 3) were randomized and controlled trials; 4) followed patients for at least one month after conclusion of therapy; and 5) assessed symptoms of nonulcer dyspepsia. Ten randomized, controlled trials from 1995-1999 that used combination therapy with proven effectiveness against *H. pylori* were included in the meta-analysis. Control therapy consisted of placebo or antisecretory therapy alone.

3. Is it unlikely that important, relevant studies were missed?

Yes. Two independent investigators reviewed Medline and HealthStar as well as abstracts from the American Gastroenterological Association, the American College of Gastroenterology, and the European *H. pylori* study Group. Reference lists were checked from all articles that met the selection criteria. Efforts were also made to identify unpublished trials from manufacturers and experts in the field, although no relevant trials were identified in this manner.

4. Was the validity of the included studies appraised?

Yes. Each article was given a score (1-5) by two independent investigators based upon the description of randomization, blinding, and patient withdrawals. There was 97% agreement between the two reviewers. Seven of the ten trials scored a rating between 3-5 and only one trial had a rating score of 1.

5. Were the assessments of studies reproducible?

Yes. A pooled random-effects estimates of odds ratios (OR) and 95% confidence intervals (CI) was calculated as described by Fleiss. (3) Tests for heterogeneity across studies were performed. A *p* value of less than 0.5 indicated statistical heterogeneity, meaning that the trials were too different to combine in a meta-analysis.

What were the Results?

1. What are the overall results of the review?

One hundred and fifty-four articles were identified, of which ten met the inclusion criteria. Seven trials including 1544 patients were used to assess the primary outcome (proportion of patients with treatment success at least 1 month after completion of eradication therapy compared to control therapy); three of these trials were in abstract form only. One of the abstracts utilized a 5 day triple therapy eradication regimen and most *H. pylori* guidelines recommend a minimum 7 day treatment period. (1) A second abstract used a double therapy regimen (amoxicillin plus omeprazole) which has an eradication success rate of 50-80% compared to 85-98% for triple and quadruple regimens.

Overall, no differences in dyspepsia symptoms were found between treatment and control groups. The OR was 1.29 (95% CI, 0.89 to 1.89, *p* = 0.18) for the 7 trials. Significant heterogeneity was found which resolved upon exclusion of one trial. The OR was 1.07 (95% CI, 0.83 to 1.37, *p* > 0.2) for

treatment success *with H. pylori* eradication for the 6 remaining trials. The trial that was excluded for heterogeneity was the only trial showing a significant result in favour of *H. pylori* eradication.

For the secondary outcome (treatment success in *H. pylori* cured patients versus those with persistent infection), the OR was 1.17 (95% CI, 0.87 to 1.59, $p>0.2$) for treatment that resulted in cure rather than persistent infection. No evidence of heterogeneity was found in the five trials used to assess this outcome.

2. How precise were the results?

Several different analyses were performed, all with similar results. Four studies that provided a specific definition of dyspepsia showed an OR for treatment success of 1.04 (CI, 0.80 to 1.35, $p>0.2$) with no evidence of heterogeneity. Four studies with the highest methodological quality (excluded the abstracts) demonstrated statistical heterogeneity with an OR of 1.41 (CI, 0.85 to 2.33, $p=0.18$). Analysis of six studies that had a follow-up period of at least a 6 months also revealed statistical heterogeneity with an OR of 1.24 (CI, 0.84 to 1.84, $p>0.2$).

Seven studies provided a scoring system to assess dyspepsia. To allow comparison of the mean scores between study groups, the mean numerical change in symptom score was divided by the maximum possible symptom score for each study. In 5 of these studies, both the raw and adjusted mean dyspepsia scores varied by less than 5 percentage points between the treatment and control groups. The smallest trial ($n=41$) showed the greatest benefit in favour of *H. pylori* therapy (decrease in score of 35% vs. 16% for control group), however this trial had the lowest methodological rating by the investigators with a score of 1.

3. How much does allowance for uncertainty change the results?

The results do not change. See number 2 above.

Will the Results Help Me in Caring for My Patients

1. Can the results be applied to my patient care?

Yes. Nonulcer dyspepsia represent a relatively common disorder with an prevalence ranging from 25 to 41%.² This meta-analysis suggests that alternate therapy to *H. pylori* eradication is advisable in patients with diagnosed nonulcer dyspepsia who do not have an underlying organic disorder, such as duodenal or gastric ulcer. Other therapy to be explored in these patients include prokinetic agents, acid suppression, psychotropic therapy, or antinociceptive therapy. (2)

2. Were all clinically important outcomes considered?

Yes.

3. Are the likely treatment benefits worth the potential harms and costs?

No. The results of this trial do not support treatment of *H. pylori* infection in diagnosed nonulcer dyspepsia. While *H. pylori* is easily detectable by urea breath test or serology, overtreatment of *H. pylori* with double or triple antibiotic regimens can lead to antibiotic resistance and increase in health care costs.

Commentary

This meta-analysis provides further support for the recommendations made by National Institute of Health in 1994⁴ that *H. pylori* should not be eradicated in diagnosed nonulcer dyspepsia. What this meta-analysis does not answer, is whether *H. pylori* should be eradicated in uninvestigated dyspepsia. Complete investigation for dyspepsia is recommended for all patients greater than 50 years of age or those who present with alarm symptoms (e.g. bleeding, weight loss, vomiting). (5) For younger patients with no alarm features and who are not receiving NSAID or present with reflux symptoms, the 2000 Canadian Dyspepsia Working Group recommend investigating for *H. pylori* and treating all positive patients; this decision is based upon the assumption that between 5-15% of these patients will have underlying peptic ulcer disease and thus benefit from eradication of the organism. (5) Further study is required to elucidate the appropriate management of uninvestigated dyspepsia.

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Therapy for *Helicobacter pylori* in Patients with Nonulcer Dyspepsia: Eradicate or Not?

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Reviewer's email address: kshalans@vanhosp.bc.ca

Reviewer's profession/specialty: Dialysis/ Residency Coordinator

Original Citation

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2. Were all clinically important outcomes considered?

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No. The results of this trial do not support treatment of *H. pylori* infection in diagnosed nonulcer dyspepsia. While *H. pylori* is easily detectable by urea breath test or serology, overtreatment of *H. pylori* with double or triple antibiotic regimens can lead to antibiotic resistance and increase in health care costs.

Commentary

This meta-analysis provides further support for the recommendations made by National Institute of Health in 1994 that *H. pylori* should not be eradicated in diagnosed nonulcer dyspepsia. What this meta-analysis does not answer is whether *H. pylori* should be

eradicated in uninvestigated dyspepsia. Complete investigation for dyspepsia is recommended for all patients greater than 50 years of age or those who present with alarm symptoms (e.g. bleeding, weight loss, vomiting). (5) For younger patients with no alarm features and who are not receiving NSAID or present with reflux symptoms, the 2000 Canadian Dyspepsia Working Group recommend investigating for *H. pylori* and treating all positive patients; this decision is based upon the assumption that between 5-15% of these patients will have underlying peptic ulcer disease and thus benefit from eradication of the organism. (5) Further study is required to elucidate the appropriate management of uninvestigated dyspepsia.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;5:210-212.

Efficacy and Safety of Recombinant Human Activated Protein C for Severe Sepsis: Can we Reduce Death Rate with an Antithrombotic, Antiinflammatory and Profibrinolytic agent?

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Reviewer: Jane de Lemos, , PharmD

Reviewer's email address: jdelemos@vanhosp.bc.ca

Reviewer's profession/specialty: Critical care

Original Citation

Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ Jr. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699-709. [PubMed Cit](#)

Overall Study Question

This study had two objectives. The first objective was to determine whether the administration of activated protein C (drotrecogin alfa activated) to patients with early severe sepsis reduced mortality at 28 days as compared with placebo. The second objective was to determine the incidence of adverse events associated with drotrecogin alfa activated. The patients had severe sepsis: documented or suspected infection with 3 or more signs of systemic inflammation and sepsis-induced failure of at least one organ or system that lasted no longer than 24 hours. These last two criteria had to be met within a 24-hour period. Outcome variables were mortality at 28 days and incidence of adverse events. The intervention was a 96-hour infusion of drotrecogin alfa activated at 24mcg/Kg/hour or a placebo.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. This was a prospective, randomized, double-blind, placebo-controlled multicenter trial involving 1,690 patients (840 received placebo, 850 received drotrecogin alfa activated). Patients were randomized in a 1:1 manner to receive drotrecogin alfa

activated or placebo (0.9% saline with or without 0.1% human serum albumin) at each centre. Block randomization stratified according to site, and all assignments were made through a central randomization centre.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. Of the 1,728 patients who underwent randomization, 1,690 received study drug or placebo. Thirty-eight patients (17 in the placebo group and 21 in the drotrecogin alfa activated group) did not receive either study drug.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. The patients, investigators and the sponsor were unaware of the patients' treatment assignment.

4. Were the groups similar at the start of the trial?

The groups were similar in terms of age, race, sex, APACHE II scores, underlying illness, type of infection (i.e. site and organism). A similar number of patients were in shock (70%) or required mechanical ventilation (>70%).

5. Aside from the experimental intervention, were the groups treated equally?

Yes. A blinded review panel judged that the patients were treated equally with respect to appropriate antibiotic treatment.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

Mortality at 28 days was 24.7% in the drotrecogin alfa activated group as compared with 30.8% in the placebo group ($p=0.005$). Therefore, the administration of drotrecogin alfa activated was associated with a 6.1% absolute risk reduction in mortality at 28 days as compared with placebo.

Prospectively defined subgroup analyses were performed for a number of baseline characteristics, including the APACHE II score, the number of dysfunctional organs or

systems, other indicators of severity of disease, sex, age, the site of infection, the type of infection (gram-positive, gram-negative or mixed) and presence or absence of protein C deficiency. A consistent effect of treatment with drotrecogin alfa was observed amongst all subgroups.

The percentage of patients who had at least one adverse event was similar in both groups; 12.5% in drotrecogin alfa activated vs. 12.1% in the placebo group ($p=0.84$). The incidence of serious bleeding was higher in the drotrecogin alfa activated group than in the placebo group (3.5% vs. 2.0% $p=0.06$).

2. How precise was the estimate of the treatment effect?

The 95% confidence interval for the 6.1% absolute reduction in mortality was 1.9-10.4.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes, with careful regard to the inclusion and exclusion criteria used in this study.

2. Were all clinically important outcomes considered?

Yes.

3. Are the likely treatment benefits worth the potential harms and costs?

Yes, for every 17 (actual NNT = 16.39) patients treated, 1 life will be saved. For every 67 patients treated, 1 patient will suffer from serious bleeding. The economic cost of drotrecogin alfa activated is not known. Currently this treatment is available in Canada on a compassionate use basis only.

Commentary

This is a very important study that has provided evidence that mortality of select patients with severe sepsis can be reduced with the administration of drotrecogin alfa activated. The study was very well conducted. Although the data was not provided, the beneficial effects of this drug were apparently consistent across different subgroups including severity of illness, number of dysfunctional organs/ systems and presence or absence of protein C deficiency (80% of patients had protein C deficiency). In order for patients to benefit from this drug, clinicians need to be alert to the timing of onset of sepsis-induced failure as drotrecogin alfa activated needs to be administered within 24 hours of this criterion. Depending on the acquisition cost, this study may have important implications for resource allocation within healthcare institutions.

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J Inform Pharmacother 2001;5:210-212.

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;5:213-215.

The International Stroke Trial: What "IS" the Best Therapy for Acute Ischaemic Stroke?

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Reviewer: Susan C. Fagan, Pharm.D., BCPS, FCCP

Reviewer's email address: sfagan@mail.mcg.edu

Reviewer's profession/specialty: Pharmacotherapy/Stroke

Original Citation

International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomized trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. Lancet 1997;349:1569-81. [PubMed Cit](#)

Overall Study Question

The IST was a large (n=19,435) international study designed to determine the safety and efficacy of two widely used treatments for acute ischaemic stroke: unfractionated heparin and aspirin. Patients with acute stroke were eligible if they could be enrolled within 48 hours after a negative CT scan to receive either heparin 5000 u sc q12h (n=2,426) or heparin 12500 u sc q12h (n=2,432) or aspirin 300 mg daily (n=2,430), both heparin and aspirin (n=2,430), or neither drug (4,860). The major endpoints of the study were death and other clinical events at 14 days, death and dependency at 6 months and intracranial and other hemorrhage.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. 99.99% of patients were complete at the 14-day evaluation and 99.2% were complete at 6 months.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

No. This trial was an open label study.

4. Were the groups similar at the start of the trial?

Unknown. The breakdown of patient characteristics by treatment group at the beginning of the trial was not given. The authors stated that groups were similar.

5. Aside from the experimental intervention, were the groups treated equally?

The use of non-trial treatments (including anti-edema, surgery and thrombolysis) was well balanced according to the authors (data not given). Thirty-six different countries may have lead to regional differences in co-intervention. However, strict randomization protocol should have taken care of any differences. The compliance rates were good (88-94% for heparin and 93% for aspirin) but it was not broken out by region.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

Patients who received aspirin had an absolute reduction in stroke recurrence at 14 days of 1.1% and there was no difference in hemorrhagic strokes. Death or nonfatal stroke at 14 days was significantly less in the aspirin group (11.3% vs. 12.4%, $p=0.02$, NNT=91).

Patients who received heparin experienced a significant reduction in stroke recurrence within 14 days by 0.9%. However, patients who received heparin also experienced an increase in hemorrhagic strokes by 0.8%(absolute)in the same time frame. The increase in hemorrhagic strokes was dose-related. There was no difference in the incidence of death or dependency at 6 months in the heparin group.

2. How precise was the estimate of the treatment effect?

Unable to extract confidence intervals from the paper.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Most clinicians have used the IST results as evidence supporting immediate initiation of aspirin in hospitalized acute ischemic stroke patients and some have used it as evidence to abandon all but rare use of full-dose unfractionated heparin in acute ischemic stroke.

2. Were all clinically important outcomes considered?

Yes. Recurrent ischaemic stroke, hemorrhagic stroke, death or nonfatal stroke, pulmonary embolism and major extracranial bleed were all assessed at 14 days. At six months, death and dependency were assessed.

3. Are the likely treatment benefits worth the potential harms and costs?

Yes, with aspirin. Aspirin appeared to provide a reduction in recurrence without significantly increasing the risk of hemorrhagic stroke. No, with subcutaneous heparin. Although the heparin prevented recurrence within 14 days, there was a significant increase in hemorrhagic stroke as well. This resulted in an overall neutral effect on death and dependency.

Commentary

When the results of the IST are combined with the results of the Chinese Acute Stroke Trial (1), one can support the recommendation to begin aspirin in all eligible acute ischemic stroke patients within 48 hours of symptom onset. The use of unfractionated heparin remains controversial. There is a strong-voiced minority who state that the IST study is flawed and patients who needed heparin were excluded (this was an exclusion criteria for this study). Also, a small number of patients did not have a CT scan prior to enrolling. This may have led to an overestimation of the risk of heparin. Even when a more easily dosed and theoretically safer "heparinoid" compound was subsequently tried in ischaemic stroke in the TOAST trial, a similar result was obtained. (2) The heparinoid did not offer any benefit, but was associated with increased risk. Despite the fact that there is still no evidence to support the use of heparin in acute ischemic stroke, it remains in use and proponents favour further clinical trials to test immediate (i.e. within 6 hours) anticoagulation with this product. (3)

References

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J Inform Pharmacother 2001;5:213-215.

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;5:216-219.

Use of Inhaled Anti-inflammatory Medications for Asthma: Are They Worth the Cost?

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Reviewer's email address: lynd@interchange.ubc.ca

Reviewer's profession/specialty: Pharmacoepidemiology/Outcomes research/Asthma (Funded by CIHR doctoral fellowship)

Original Citation

Ozminkowski RJ, Wang S, Marder WD, Azzolini J, Schutt D. Cost implications for the use of inhaled anti-inflammatory medications in the treatment of asthma. Pharmacoeconomics 2000;18:253-264. [PubMed Cit](#)

Overall Study Question

The objective of this study was to compare the expected costs of treating patients with asthma with, versus without, inhaled anti-inflammatory medications (i.e. corticosteroids, sodium cromoglycate, nedocromil), while attempting to adjust for other factors that also influence medical care expenditures. The study population was comprised of 7,466 patients continuously enrolled in one of 35 health plans in the United States in 1995 and 1996. These health plans were offered by 10 large employers who contributed inpatient, outpatient, pharmaceutical and health plan enrollment data to the MEDSTAT Group Marketscan Family of databases. Therefore, this study is based entirely on administrative health plan data. The effect of inhaled anti-inflammatory medications on two outcomes was evaluated: total inpatient, outpatient, and pharmaceutical expenditures, and asthma-related expenditures, in the 1996 calendar year. Simulation models were used to determine the differences in costs assuming all patients were, or were not, treated with an anti-inflammatory medication.

Are the Results of the Study Valid?

1. Did the analysis provide a full economic comparison of health care strategies?

This study does not provide a full comparison of economic strategies, and does not calculate any incremental costs associated with any particular treatment. Outcomes were not measured. The authors suggest that this study was done "from the perspective of the payer, and to some extent, the patient". They suggest that the perspective of the patient is taken, given that they include any co-payment and deductible in their determination of costs. In essence, this is a budget impact study, however, the inclusion of any co-pay and deductible amounts in the "costs" deems it an inaccurate assessment of the true budget impact from the perspective of the payer. Furthermore, from the perspective of the patient, this approach captures only a fraction of the costs borne by the patient.

2. Were the costs and outcomes properly measured and valued?

Outcomes were not valued, nor differences in outcomes between treatment groups (i.e. hospital admission, emergency visits, etc.) valued or assessed. The authors do not explicitly state how "costs" were determined. However, it can be assumed that "costs" were derived from the MarketScan databases, and therefore, insurance claims were used to determine all "costs" associated with treatment. However, these claims databases are unlikely to measure costs, but rather more likely track charges. Charges may differ significantly for similar patients, depending on the patient's insurance provider. Therefore, it would appear that this study was actually measuring charges as opposed to costs, but it is not clear whether or not these charges were consistent across all 35 health plans.

3. Was appropriate allowance made for uncertainties in the analysis?

Data were analyzed using nonlinear exponential regression to estimate the relationships between medical care expenditures in 1996 and the use of inhaled anti-inflammatory drugs. Mean and median costs, as well as standard deviations are reported. Cost differences between patients treated and not treated with inhaled anti-inflammatory medications were tested for statistical significance, as was the model simulating all patients treated versus not treated with an inhaled anti-inflammatory medications. Although standard deviations on all costs were reported, sensitivity analysis was not performed.

4. Are estimates of costs and outcomes related to the baseline risk in the treatment population?

Sub-group analyses were not performed. Although Adjusted Clinical Group (ACG) was used to control for disease severity in the multivariate regression analysis, costs associated with treating patients with different disease severities was not reported. The effects of drug therapy on the different costs (i.e. inpatient, outpatient, or pharmaceutical costs) were not provided.

What were the Results?

1. What were the incremental costs and outcomes of each strategy?

Incremental costs were not calculated. All costs were valued in US dollars. The mean total health care expenditure in patients treated with inhaled anti-inflammatory drugs was \$4,534.08 (median \$2,300.91; SD \$8,827.56) versus \$3,897.54 (median \$1,329.04; SD \$13,187.99) for patients not receiving an anti-inflammatory medication. The difference in mean cost was not statistically significant, however the median cost was significantly lower in those patients who did not receive an inhaled anti-inflammatory medication. Analysis of asthma-related costs yielded similar results. The median asthma-related cost was \$453.23 for anti-inflammatory treated patients versus \$99.63 for patients not treated with an inhaled anti-inflammatory medication ($p=0.01$). However, those patients not treated with anti-inflammatory medications ($n=2,242$) differed significantly from those treated with anti-inflammatory medications on a number of variables, including type of insurance plan, age, geographic region, and the primary policy holder in the family. This would suggest that these two groups are systematically different, and therefore any differences in costs of disease management cannot be attributed solely to differences in use of anti-inflammatory medications.

The results of the regression modeling and simulation showed that the estimated mean total health care expenditure per person, if all patients in the sample received an inhaled anti-inflammatory, would be \$2,954.96, versus \$3,899.78 if no patients were treated with inhaled anti-inflammatory drugs. Thus, overall health care costs would decrease by \$944.82 per patient. Conversely, when only asthma-related expenditures were evaluated, if all patients were treated with an inhaled anti-inflammatory, total asthma related costs were estimated to be \$940.36 per patient versus \$441.74 per patient if nobody was treated with an inhaled anti-inflammatory. Therefore, asthma management with inhaled anti-inflammatory drugs would result in \$498.74 greater expenditure per patient.

However, as discussed in the first analysis, those treated and not treated with anti-inflammatory drugs are not comparable on a number of different variables. Although these variables were included in the multivariate regression, it is likely that patients treated versus not treated with inhaled anti-inflammatory drugs were systematically different in other drug management and cost of care aspects that were not measured and may have been, in fact, immeasurable. Further support of this is provided by the assessment of model fit, particularly for the regression determining relationships with asthma-related health costs. The final model resulted in an adjusted r-square of only 0.038. Although the model was significant, this suggests that this model describes very little of the variance associated with asthma-related health care costs.

2. Do incremental costs and outcomes differ between sub-groups?

Sub-group analyses were not performed.

3. How much does allowance for uncertainty change the results?

Although results of any sensitivity analyses were not provided, the variance of the total and asthma-related costs was large. The standard deviations for the mean total and the asthma-related costs for patients treated with anti-inflammatory medications were \$8,827.56 and \$2,275.25, respectively. The corresponding standard deviations in costs for patients not treated with anti-inflammatory medications were \$13,187.99 and \$1,930.55. This suggests two plausible outcomes: that there was the potential for the results to be reversed, and that there was significant heterogeneity within the groups in terms of total and asthma-related health costs. This provides further evidence of systematic differences between the groups.

Will the results help me in caring for my patients?

1. Are the treatment benefits worth the harms and costs?

The results suggest dominance of using anti-inflammatory medications, at least in terms of total health care costs. Outcomes were not measured, so harm could not be assessed. The perspective of this analysis and the limitations of the data as outlined previously limit the applicability of the results. The true costs of the administration of inhaled anti-inflammatory drugs thus remains to be determined.

2. Could my patients expect similar health outcomes?

Outcomes were not measured.

3. Could I expect similar costs?

These data were derived from administrative health care records, and therefore more likely reflect charges as opposed to costs. Furthermore, this was a US-based study of 35 health insurers; charges for similar procedures or medications may have differed between insurers, but this was not delineated in the publication. The inclusion criteria for the study limited the eligibility to patients to those who were likely to have more severe disease. Therefore, these results cannot be extrapolated to any other setting. Considering all study limitations, the true impact of using inhaled anti-inflammatory medications on both total costs of health care, and asthma-related costs, remains in question.

Commentary

It is well established that inhaled anti-inflammatory medications, particularly corticosteroids, should be the mainstay of therapy in all but the mildest asthmatics. This is based on ample evidence of improved outcomes in patients treated with appropriate doses of inhaled corticosteroids compared to those who continue to rely on short-acting beta-agonists. Clinical improvements associated with appropriate use of inhaled corticosteroids include reduction in symptom severity, improvement in peak flow and other objective spirometric measures of lung function, decreased airway hyperresponsiveness, prevention of

exacerbations, and possibly the prevention of airway remodeling. These benefits are expected to be accompanied by increased drug costs; other outpatient and inpatient costs are expected to decrease while other economic implications, including quality of life and indirect costs such as time off work, are expected to improve. This study did not stratify costs to allow for the determination of whether increased drug costs resulted in decreased inpatient and outpatient costs. The primary methodologic limitations of this study include: 1) the heterogeneity of patients receiving and not receiving inhaled anti-inflammatory medications; 2) the use of charges versus costs, and the lack of providing explicitly how costs were determined; 3) inclusion criteria limited to patients who likely have moderate to severe disease; 4) a poor model fit in the determination of factors associated with asthma related costs; and 5) the lack of breakdown of inpatient, outpatient, and pharmaceutical costs associated with each treatment. Therefore, the apparent greater asthma-related costs associated with inhaled anti-inflammatory use remains questionable.

Given the known benefits of inhaled corticosteroid administration and their inclusion as the mainstay of therapy in the current asthma management guidelines, this study should in no way impact the decision of whether or not to prescribe an inhaled anti-inflammatory medication.

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Use of Inhaled Anti-inflammatory Medications for Asthma: Are They Worth the Cost?

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Reviewer's profession/specialty: Pharmacoepidemiology/Outcomes research/Asthma (Funded by CIHR doctoral fellowship)

Original Citation

Ozminkowski RJ, Wang S, Marder WD, Azzolini J, Schutt D. Cost implications for the use of inhaled anti-inflammatory medications in the treatment of asthma. *Pharmacoeconomics* 2000;18:253-264.

Overall Study Question

The objective of this study was to compare the expected costs of treating patients with asthma with, versus without, inhaled anti-inflammatory medications (i.e. corticosteroids, sodium cromoglycate, nedocromil), while attempting to adjust for other factors that also influence medical care expenditures. The study population was comprised of 7,466 patients continuously enrolled in one of 35 health plans in the United States in 1995 and 1996. These health plans were offered by 10 large employers who contributed inpatient, outpatient, pharmaceutical and health plan enrollment data to the MEDSTAT Group MarketScan Family of databases. Therefore, this study is based entirely on administrative health plan data. The effect of inhaled anti-inflammatory medications on two outcomes was evaluated: total inpatient, outpatient, and pharmaceutical expenditures, and asthma-related expenditures, in the 1996 calendar year. Simulation models were used to determine the differences in costs assuming all patients were, or were not, treated with an anti-inflammatory medication.

Are the Results of the Study Valid?

1. Did the analysis provide a full economic comparison of health care strategies?

This study does not provide a full comparison of economic strategies, and does not calculate any incremental costs associated with any particular treatment. Outcomes were not measured. The authors suggest that this study was done "from the perspective of the payer, and to some extent, the patient". They suggest that the perspective of the patient is taken, given that they include any co-payment and deductible in their determination of costs. In essence, this is a budget impact study, however, the inclusion of any co-pay and deductible amounts in the "costs" deems it an inaccurate assessment of the true budget impact from the perspective of the payer. Furthermore, from the perspective of the patient, this approach captures only a fraction of the costs borne by the patient.

2. Were the costs and outcomes properly measured and valued?

Outcomes were not valued, nor differences in outcomes between treatment groups (i.e. hospital admission, emergency visits, etc.) valued or assessed. The authors do not explicitly state how "costs" were determined. However, it can be assumed that "costs" were derived from the MarketScan databases, and therefore, insurance claims were used to determine all "costs" associated with treatment. However, these

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claims databases are unlikely to measure costs, but rather more likely track charges. Charges may differ significantly for similar patients, depending on the patient's insurance provider. Therefore, it would appear that this study was actually measuring charges as opposed to costs, but it is not clear whether or not these charges were consistent across all 35 health plans.

3. Was appropriate allowance made for uncertainties in the analysis?

Data were analyzed using nonlinear exponential regression to estimate the relationships between medical care expenditures in 1996 and the use of inhaled anti-inflammatory drugs. Mean and median costs, as well as standard deviations are reported. Cost differences between patients treated and not treated with inhaled anti-inflammatory medications were tested for statistical significance, as was the model simulating all patients treated versus not treated with an inhaled anti-inflammatory medications. Although standard deviations on all costs were reported, sensitivity analysis was not performed.

4. Are estimates of costs and outcomes related to the baseline risk in the treatment population?

Sub-group analyses were not performed. Although Adjusted Clinical Group (ACG) was used to control for disease severity in the multivariate regression analysis, costs associated with treating patients with different disease severities was not reported. The effects of drug therapy on the different costs (i.e. inpatient, outpatient, or pharmaceutical costs) were not provided.

What were the Results?

1. What were the incremental costs and outcomes of each strategy?

Incremental costs were not calculated. All costs were valued in US dollars. The mean total health care expenditure in patients treated with inhaled anti-inflammatory drugs was \$4,534.08 (median \$2,300.91; SD \$8,827.56) versus \$3,897.54 (median \$1,329.04; SD \$13,187.99) for patients not receiving an anti-inflammatory medication. The difference in mean cost was not statistically significant, however the median cost was significantly lower in those patients who did not receive an inhaled anti-inflammatory medication. Analysis of asthma-related costs yielded similar results. The median asthma-related cost was \$453.23 for anti-inflammatory treated patients versus \$99.63 for patients not treated with an inhaled anti-inflammatory medication ($p=0.01$). However, those patients not treated with anti-inflammatory medications ($n=2,242$) differed significantly from those treated with anti-inflammatory medications on a number of variables, including type of insurance plan, age, geographic region, and the primary policy holder in the family. This would suggest that these two groups are systematically different, and therefore any differences in costs of disease management cannot be attributed solely to differences in use of anti-inflammatory medications.

The results of the regression modeling and simulation showed that the estimated mean total health care expenditure per person, if all patients in the sample received an inhaled anti-inflammatory, would be \$2,954.96, versus \$3,899.78 if no patients were treated with inhaled anti-inflammatory drugs. Thus, overall health care costs would decrease by \$944.82 per patient. Conversely, when only asthma-related expenditures were evaluated, if all patients were treated with an inhaled anti-inflammatory, total asthma related costs were estimated to be \$940.36 per patient versus \$441.74 per patient if nobody was treated with an inhaled anti-inflammatory. Therefore, asthma management with inhaled anti-inflammatory drugs would result in \$498.74 greater expenditure per patient.

However, as discussed in the first analysis, those treated and not treated with anti-inflammatory drugs are not comparable on a number of different variables. Although these variables were included in

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the multivariate regression, it is likely that patients treated versus not treated with inhaled anti-inflammatory drugs were systematically different in other drug management and cost of care aspects that were not measured and may have been, in fact, immeasurable. Further support of this is provided by the assessment of model fit, particularly for the regression determining relationships with asthma-related health costs. The final model resulted in an adjusted r-square of only 0.038. Although the model was significant, this suggests that this model describes very little of the variance associated with asthma-related health care costs.

2. Do incremental costs and outcomes differ between sub-groups?

Sub-group analyses were not performed.

3. How much does allowance for uncertainty change the results?

Although results of any sensitivity analyses were not provided, the variance of the total and asthma-related costs was large. The standard deviations for the mean total and the asthma-related costs for patients treated with anti-inflammatory medications were \$8,827.56 and \$2,275.25, respectively. The corresponding standard deviations in costs for patients not treated with anti-inflammatory medications were \$13,187.99 and \$1,930.55. This suggests two plausible outcomes: that there was the potential for the results to be reversed, and that there was significant heterogeneity within the groups in terms of total and asthma-related health costs. This provides further evidence of systematic differences between the groups.

Will the Results Help Me in Caring for My Patients?

1. Are the treatment benefits worth the harms and costs?

The results suggest dominance of using anti-inflammatory medications, at least in terms of total health care costs. Outcomes were not measured, so harm could not be assessed. The perspective of this analysis and the limitations of the data as outlined previously limit the applicability of the results. The true costs of the administration of inhaled anti-inflammatory drugs thus remains to be determined.

2. Could my patients expect similar health outcomes?

Outcomes were not measured.

3. Could I expect similar costs?

These data were derived from administrative health care records, and therefore more likely reflect charges as opposed to costs. Furthermore, this was a US-based study of 35 health insurers; charges for similar procedures or medications may have differed between insurers, but this was not delineated in the publication. The inclusion criteria for the study limited the eligibility to patients to those who were likely to have more severe disease. Therefore, these results cannot be extrapolated to any other setting. Considering all study limitations, the true impact of using inhaled anti-inflammatory medications on both total costs of health care, and asthma-related costs, remains in question.

Commentary

It is well established that inhaled anti-inflammatory medications, particularly corticosteroids, should be the mainstay of therapy in all but the mildest asthmatics. This is based on ample evidence of improved outcomes in patients treated with appropriate doses of inhaled corticosteroids compared to those who continue to rely on short-acting beta-agonists. Clinical improvements associated with appropriate use of inhaled corticosteroids include reduction in symptom severity, improvement in peak flow and other objective spirometric measures of lung function, decreased airway hyperresponsiveness,

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prevention of exacerbations, and possibly the prevention of airway remodeling. These benefits are expected to be accompanied by increased drugs costs; other outpatient and inpatient costs are expected to decrease while other economic implications, including quality of life and indirect costs such as time off work, are expected to improve. This study did not stratify costs to allow for the determination of whether increased drug costs resulted in decreased inpatient and outpatient costs. The primary methodologic limitations of this study include: 1) the heterogeneity of patients receiving and not receiving inhaled anti-inflammatory medications; 2) the use of charges versus costs, and the lack of providing explicitly how costs were determined; 3) inclusion criteria limited to patients who likely have moderate to severe disease; 4) a poor model fit in the determination of factors associated with asthma related costs; and 5) the lack of breakdown of inpatient, outpatient, and pharmaceutical costs associated with each treatment. Therefore, the apparent greater asthma-related costs associated with inhaled anti-inflammatory use remains questionable.

Given the known benefits of inhaled corticosteroid administration and their inclusion as the mainstay of therapy in the current asthma management guidelines, this study should in no way impact the decision of whether or not to prescribe an inhaled anti-inflammatory medication.

J Inform Pharmacother 2001;5:216-219.

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;5:220-222.

Oral Amiodarone for Prevention of Atrial Fibrillation after Open Heart Surgery: Does a Fist Beat Scissors?

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Original Citation

Giri S, White CM, Dunn AB, Felton K, Freeman-Bosco L, Reddy P, Tsikouris JP, Wilcox HA, Kluger J. Oral amiodarone for prevention of atrial fibrillation after open heart surgery, the Atrial Fibrillation Suppression Trial (AFIST): a randomised placebo-controlled trial. Lancet 2001;357:830-6. [PubMed Cit](#)

Overall Study Question

The AFIST trial was a prospective, randomized, placebo-controlled study undertaken in a 600-bed tertiary care center to assess the safety and efficacy of a brief oral amiodarone regimen for prevention of post cardiac surgery atrial fibrillation (AF) in patients 60 years and older already receiving beta-blockers. Patients were included if they were at least 60 years old, in normal sinus rhythm (NSR), hemodynamically stable (SBP >90 mm Hg), had a normal baseline QTc < 440 msec, and were available at least 1 day prior to scheduled cardiopulmonary bypass surgery. Patients were excluded if they had chronic AF, myocardial infarction within the past 3 weeks, HR <45 bpm, advanced heart block, automatic implantable defibrillator, a history of amiodarone toxicity, untreated thyroid disease, hepatic transaminases greater than four times normal, and interacting drugs. Patients were randomized to receive either a slow or fast oral loading regimen of amiodarone or matching placebo prior to surgery and continued for four days post-op. The primary outcome was the incidence of any post-operative AF lasting longer than 5 minutes during the 30-day follow-up.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. During a 14-month period, 1,430 patients undergoing angiography for ischemic heart or valvular disease were screened using consecutive sampling. A computer-generated randomization table was used to assign patients to either a slow load or fast load group with each group stratified by presence or absence of valvular surgery. The slow load group (≥ 5 days before surgery) received oral amiodarone 200 mg daily for 5 days before surgery, 400 mg twice daily on the day of surgery, and 400 mg twice daily on post-op days 1-4 or matching placebo. The fast load group (< 5 but > 1 day before surgery) received 400 mg four times daily for 1 day, 600 mg twice daily on the day of surgery, and 400 mg twice daily on post-op days 1-4 or matching placebo.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. One thousand four hundred and thirty patients were screened and 379 patients met the study criteria. Reasons for ineligibility were provided. Of the 379 eligible patients, 220 were randomized – 120 in the amiodarone group and 100 in the placebo group. The primary outcome was analyzed using the intention to treat principle and no patients were lost to follow-up. Drug withdrawal in the amiodarone and placebo groups was 6.7% and 5%, and overall in-hospital mortality and 30-day mortality rates were 2.3% and 3.6%.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. The randomization schedule was sealed in opaque envelopes and kept in the central pharmacy. Only the investigational pharmacist and the unmarked study administrator had knowledge of treatment group allocation, and neither had patient contact nor extracted data. All treatment regimens were double-blinded and an identical matching placebo was used.

4. Were the groups similar at the start of the trial?

Yes. Overall, patients in the experimental and control groups had similar baseline demographic and clinical characteristics, however more patients in the amiodarone group had had a previous MI.

5. Aside from the experimental intervention, were the groups treated equally?

Yes. All surgical and medical procedures were standardized using a predefined critical pathway. The surgical intervention for each group was similar except that patients in the amiodarone group had a slower heart rate during surgery and required fewer intra-operative defibrillations to restore NSR after cross-clamp release. The only co-intervention explicitly stated that was left to the discretion of physicians was the antiarrhythmic treatment of post-op AF.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

The overall risk any AF in the 30-d post op period was 23% in the amiodarone group and 38% in the placebo group ($p=0.01$), ARR = 15.5% (3.4%-27.6%), NNT = 7 (4-30). Secondary analyses revealed the rate of symptomatic AF was 4% in the amiodarone group and 18% in the placebo group ($p=0.001$), ARR = 13.8% (5.5%-22.2%), NNT = 8 (5-19). Recurrent AF was 9% in the amiodarone group and 20% in the placebo group ($p=0.02$), ARR = 10.9% (1.5%-20.2%), NNT = 10 (5-69). The rate of ventricular tachycardia (>30 seconds) and cerebrovascular accidents (CVA) was 1.7% in the amiodarone group and 7.0% in the placebo group ($p=0.04$), ARR = 5.3% (0.2%-10.8%), NNT = 19 (9-556).

There were no differences in withdrawal rates due to adverse effects in either group, and there were no differences in bradycardia, heart block, need for pacing, hypotension, or tolerability of upward titration of post-op BB therapy. There was a trend towards more nausea in the amiodarone group (27% vs. 16%, $p=0.056$). There were no differences in percentage of patients in NSR at discharge, duration of ICU stay, hospital stay, in-hospital mortality, 30-day mortality, or treatment costs between the groups.

2. How precise was the estimate of the treatment effect?

For the primary outcome of any atrial fibrillation and secondary outcomes of symptomatic AF and recurrent AF, the ARR did not cross zero, and the confidence intervals around the point estimate were narrow and represent a clinically significant result. For the analyses of ventricular tachycardia and CVA, the confidence intervals also did not cross zero, however the intervals were wide meaning the clinical significance can be questioned.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. Based on the AFIST trial, pre-operative oral amiodarone begun at least 1 day pre-op and continued for 4 days post-op can reduce any AF, symptomatic AF, and recurrent AF in patients >60 years old (mean 73 years) receiving pre-operative (mean = 89%) beta-blockers continued post-operatively. This is the first trial comparing the effects of administering an antiarrhythmic drug pre-operatively to eligible patients already receiving the gold standard of pre-op/post-op BB prophylaxis. These data should not be extrapolated to younger patients not receiving pre/post-op beta-blockers as the underlying event rate of atrial fibrillation in these groups would be different.

2. Were all clinically important outcomes considered?

Yes. Although this trial was underpowered to examine the effect of adding amiodarone to the subgroup of patients who all received beta-blockers, it did determine the effect of adding amiodarone to a group of elderly post cardiac surgery patients in whom pre-op/post-op beta blocker prophylaxis was attempted. Along with the surrogate endpoint of development of post-op AF, other valuable morbidity, mortality, and cost endpoints were evaluated in secondary analyses. Although adverse drug reactions were prospectively evaluated and surveyed, the trial was underpowered to detect rare, but clinically important adverse effects such as acute lung injury and ARDS.

3. Are the likely treatment benefits worth the potential harms and costs?

Yes. The benefits of reduction of any AF, symptomatic AF, and recurrent AF are clinically important in this population, however a larger trial would be required to clarify the ultimate impact of AF prevention on important benefits such as incidence of CVA, length of stay, and economic outcomes. Careful long-term follow up of post cardiac surgery patients receiving amiodarone will still be warranted to monitor for rare pulmonary toxicities.

Commentary

AF is a common complication of cardiac surgery and is associated with a significant impact on symptoms, morbidity, and health care costs. Pre-operative and/or post-operative beta blocker therapy is the gold standard for prevention of post cardiac surgery AF, however, antiarrhythmic agents such as amiodarone and sotalol have also been studied for prevention. Conflicting results from studies on the efficacy of amiodarone prophylaxis can be explained by differences in study populations, prophylactic regimens, underutilization of proven beta blocker prophylaxis, and a falsely elevated AF rates due to post-op beta blocker withdrawal in some patients.

The AFIST trial is the first trial specifically designed to evaluate the effectiveness of prophylactic amiodarone added to gold standard BB therapy in an elderly population, and reports significant reductions in post cardiac surgery AF. These benefits are both statistically significant and clinically important. Larger trials will be needed to clarify the impact of this surrogate outcome on more important morbidity and economic outcomes such as incidence of CVA and cost effectiveness of amiodarone prophylaxis. Judicious monitoring of patients receiving any amiodarone prophylaxis regimen should continue due to the potential for rare pulmonary toxicities.

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Oral Amiodarone for Prevention of Atrial Fibrillation after Open Heart Surgery: Does a Fist Beat Scissors?

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Reviewer's profession/specialty: Pharmacotherapeutic Specialist/Critical Care

Original Citation

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6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

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2. Were all clinically important outcomes considered?

Yes. Although this trial was underpowered to examine the effect of adding amiodarone to the subgroup of patients who all received beta-blockers, it did determine the effect of adding amiodarone to a group of elderly post cardiac surgery patients in whom pre-op/post-op beta blocker prophylaxis was attempted. Along with the surrogate endpoint of development of post-op AF, other valuable morbidity, mortality, and cost endpoints were evaluated in secondary analyses. Although adverse drug reactions were prospectively evaluated and surveyed, the trial was underpowered to detect rare, but clinically important adverse effects such as acute lung injury and ARDS.

3. Are the likely treatment benefits worth the potential harms and costs?

Yes. The benefits of reduction of any AF, symptomatic AF, and recurrent AF are clinically important in this population, however a larger trial would be required

to clarify the ultimate impact of AF prevention on important benefits such as incidence of CVA, length of stay, and economic outcomes. Careful long-term follow up of post cardiac surgery patients receiving amiodarone will still be warranted to monitor for rare pulmonary toxicities.

Commentary

AF is a common complication of cardiac surgery and is associated with a significant impact on symptoms, morbidity, and health care costs. Pre-operative and/or post-operative beta-blocker therapy is the gold standard for prevention of post cardiac surgery AF, however, antiarrhythmic agents such as amiodarone and sotalol have also been studied for prevention. Conflicting results from studies on the efficacy of amiodarone prophylaxis can be explained by differences in study populations, prophylactic regimens, underutilization of proven beta blocker prophylaxis, and a falsely elevated AF rates due to post-op beta blocker withdrawal in some patients.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;5:223-225.

Green Tea and the Risk of Gastric Cancer in Japan; Is there Any Relationship or Are We Simply Reading Tea Leaves?

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Original Citation

Yoshitaka Tsubono, Yoshikazu Nishino, Shoko Komatsu, Chung-Cheng Hsieh, Seiki Kanemura, Ichiro Tsuji, Haruo Nakatsuka, Akira Fukao, Hiroshi Satoh, Shigeru Hisamichi. Green Tea and the Risk of Gastric Cancer in Japan. N Engl J Med 2001;344:632-6. [PubMed Cit](#)

Overall Study Question

The polyphenols in green tea are believed to have anticarcinogenic effects. The objective of this study was to examine whether consumption of green tea decreases the relative risk of gastric cancer.

This was a prospective cohort study involving 26,311 residents aged 40 years or older who were of Miyagi Prefecture (an area in northern Japan where the incidence of gastric cancer is high) during the period January 1984 to December 1992. A multivariate analysis that adjusted for sex, age, history of peptic ulcer, smoking status, alcohol consumption, several dietary elements, and type of health insurance was conducted to determine the relative risk of gastric cancer associated with 3 levels of green tea consumption: 1-2 cups/day, 3-4 cups/day, and ≥ 5 cups/day. There was no actual intervention. This was a population study where exposure data was gathered via self-administered questionnaires. The questionnaires were delivered to and collected from residences by government health-promotion committee members. Follow-up data on patient status and cancer incidence was gathered from population registries and the Miyagi Prefectural Cancer Registry.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

No. The self-administered questionnaires were delivered to 33,453 residents aged 40 years or greater, residing in any of 3 municipalities in Miyagi Prefecture. As there is no mention of any selection criteria (other than the aforementioned age), for these residents, it seems that the questionnaire was offered to all residents meeting the above description. This however, is not directly identified in the paper.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Unable to determine. Although all subjects entering the study were clearly accounted for (33,453 offered questionnaires; 94% returned; 31,345 usable; 30,804 did not have pre-existing cancer; 26,311 answered the green tea question on the questionnaire), the results are reported in person-years. Since subjects were followed until date of gastric cancer diagnosis, date of emigration from the study district, date of death, or end date of the study period, there is insufficient data provided to verify the number of person-years. To their credit, the authors do reveal that an evenly distributed 16% of subjects fell into the 'emigration from study district' category and were thus considered lost to follow-up.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

There were no treatment groups in this study. The questionnaire provided to subjects included questions on various health and diet habits so they were not aware that green tea specifically was being examined.

4. Were the groups similar at the start of the trial?

Since this was a population study, there were no study groups, per se. Once data on green tea consumption was available, the subjects who reportedly drank <1 cup/day were deemed the control group. Although p values are not reported, it is evident from the percentages reported in the demographics table that there were obvious differences in several habits between men and women, as well as within each sex. Some elements that differed included: pickled vegetable consumption (risk), fruit consumption (protectant), and smoking (risk).

5. Aside from the experimental intervention, were the groups treated equally?

Data was collected in the same manner for all subjects.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

The investigators found no inverse association between green tea consumption and gastric cancer risk. Relative risk was calculated for men, women, and the combination of men and women. In each of these groups, three different ratios were calculated for each of the different levels of green tea consumption: 1) sex and age adjusted; 2) multivariate: sex, age, health insurance, peptic ulcer history, smoking and diet adjusted; and finally, 3) the same multivariate analysis excluding subjects with gastric cancer diagnosed during the first 3 years of follow-up.

All but one of the 27 relative risk ratios calculated had 95% confidence intervals that contained unity. The age-adjusted relative risk for men who consumed at least 5 cups/day was 1.6 (95% confidence interval 1.1-2.2). Only the age-adjusted trend towards increased gastric cancer in men with increasing levels of green tea consumption reached statistical significance ($p=0.007$). This would imply that green tea actually increased the relative risk of gastric cancer for this stratification. When the multivariate analysis was conducted, the authors reported that the trend was still significant ($p=0.03$), however all reported relative risk ratios were associated with 95% confidence intervals that included unity. The authors concluded that this study found no association (inverse or otherwise) between green tea consumption and the risk of gastric cancer in Japan.

The authors identified some possible confounding factors that could limit this study. For example, there was no attempt to record other dietary habits or history of *Helicobacter pylori* infection. Other potential confounders that were not discussed include drugs, vitamins, herbal remedies, and other complementary therapies.

Finally, while this study spanned a 8-year period, the dietary and health habit information was apparently collected in the first year only. In contrast, the gastric cancer data was collected during the 1984 to 1992 period. Accordingly, it is possible that the dietary health and habits of the participants changed over the course of the follow-up period, although this would not have been recorded by the investigators.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Despite the potential for unmeasured confounders (including changes in dietary and/or health habits over the 9-year follow-up period), this study provides data that is often non-existent for other dietary/complementary therapies. This prospective cohort study carries more weight than case-control studies and anecdotal reports. In the absence of an intervention study, this is about as good as it gets.

The accompanying editorial (1) describes how gastric cancer characteristics are different (in

terms of location and some risk factors), between Japan and Western nations. This should be taken into consideration and mentioned during patient counseling sessions.

2. Were all clinically important outcomes considered?

The gastric cancers identified were not characterized in terms of location in the stomach (i.e. proximal vs. distal). Had this been done, the results would have greater external validity. As discussed earlier, controlling for some of the potential confounding variables would also have strengthened the study results.

3. Are the likely treatment benefits worth the potential harms and costs?

This study did not find any benefit of lowered relative risk of gastric cancer (indeed, there was a trend towards a worsening) with increasing green tea consumption. Based on the theory of the health benefits of green tea (including antioxidant activity and potential antiangiogenesis activity (2)), and the limitations of this study, green tea consumption as a beverage generally need not be discouraged.

Commentary

Many patients, especially those with cancer, have questions about dietary and complementary therapies. Often, there is only theory or anecdotal reports from which to try to formulate answers. Green tea is an antioxidant with free radical scavenging ability greater than vitamin E.(3) Generally antioxidants are considered desirable. There are however, some possible interactions between antioxidants and radiation therapy as well as between antioxidants and some chemotherapy agents.(3,4)

Unless it is decaffeinated, green tea contains about 60mg caffeine/cup. Adverse effects can include stomach upset, constipation, as well as the usual effects of caffeine. There are also potential drug and disease interactions, which are generally related to the caffeine content as well.(2)

Taking all of this into consideration, it seems that moderation would be the logical answer. Patients may be counseled on both the potential advantages and disadvantages so that they are more able to make their own informed decision about how much green tea they wish to consume. For cancer patients undergoing radiation therapy or chemotherapy with an agent whose mechanism relies on oxidation, it would be prudent to suggest abstention from or minimization of concurrent green tea consumption.

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The Journal of Informed Pharmacotherapy

Green Tea and the Risk of Gastric Cancer in Japan; Is there Any Relationship or Are We Simply Reading Tea Leaves?

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Original Citation

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Overall Study Question

The polyphenols in green tea are believed to have anticarcinogenic effects. The objective of this study was to examine whether consumption of green tea decreases the relative risk of gastric cancer.

This was a prospective cohort study involving 26,311 residents aged 40 years or older who were of Miyagi Prefecture (an area in northern Japan where the incidence of gastric cancer is high) during the period January 1984 to December 1992. A multivariate analysis that adjusted for sex, age, history of peptic ulcer, smoking status, alcohol consumption, several dietary elements, and type of health insurance was conducted to determine the relative risk of gastric cancer associated with 3 levels of green tea consumption: 1-2 cups/day, 3-4 cups/day, and ≥ 5 cups/day. There was no actual intervention. This was a population study where exposure data was gathered via self-administered questionnaires. The questionnaires were delivered to and collected from residences by government health-promotion committee members. Follow-up data on patient status and cancer incidence was gathered from population registries and the Miyagi Prefectural Cancer Registry.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

No. The self-administered questionnaires were delivered to 33,453 residents aged 40 years or greater, residing in any of 3 municipalities in Miyagi Prefecture. As there is no mention of any selection criteria (other than the aforementioned age), for these residents, it seems that the questionnaire was offered to all residents meeting the above description. This however, is not directly identified in the paper..

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Unable to determine. Although all subjects entering the study were clearly accounted for (33,453 offered questionnaires; 94% returned; 31,345 usable; 30,804 did not have pre-existing cancer; 26,311 answered the green tea question on the questionnaire), the results are reported in person-years. Since subjects were followed until date of gastric cancer diagnosis, date of emigration from the study district, date of death, or end date of the study period, there is insufficient data provided to verify the number of person-years. To their credit, the authors do reveal that an evenly distributed 16% of subjects fell into the 'emigration from study district' category and were thus considered lost to follow-up.

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3. Were patients, their clinicians, and study personnel 'blind' to treatment?

There were no treatment groups in this study. The questionnaire provided to subjects included questions on various health and diet habits so they were not aware that green tea specifically was being examined.

4. Were the groups similar at the start of the trial?

Since this was a population study, there were no study groups, per se. Once data on green tea consumption was available, the subjects who reportedly drank <1 cup/day were deemed the control group. Although p values are not reported, it is evident from the percentages reported in the demographics table that there were obvious differences in several habits between men and women, as well as within each sex. Some elements that differed included: pickled vegetable consumption (risk), fruit consumption (protectant), and smoking (risk).

5. Aside from the experimental intervention, were the groups treated equally?

Data was collected in the same manner for all subjects.

6. Overall, are the results of the study valid?

Yes.

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Issues in Pharmacotherapy Practice

Hypotension Associated with Acetaminophen Administration in the Critically-ill: Another Reason Not to Treat a Fever?

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Abstract

Fever is part of the febrile response to inflammation or infection which is an adaptive process with physiologic benefit. Although antipyretics are frequently administered to treat fever in the critically ill some clinicians have advocated against this routine practice and advocate for a careful evaluation of the risks and benefits of treating a fever to established need in each case. In light of recent reports of hypotension following acetaminophen administration, the argument against treating a fever in the critically ill may have further justification. This paper describes a case of possible acetaminophen-induced hypotension in a critically-ill patient and discusses the potential association between this relationship.

J Inform Pharmacother 2001;5:300-305.

Introduction

Although antipyretics are frequently administered to treat fever in the critically ill, many authors have advocated against this routine practice (1-4). Instead, they argue, a careful evaluation of the risks and benefits of treating a fever should be established in each case. In light of recent reports of hypotension following acetaminophen administration, the argument against treating a fever in the critically ill may have further justification (5-7).

The thermometric definition of fever is arbitrary and depends upon the purpose for which it is defined. For the purpose of warranting diagnostic investigation, the Society of Critical Care Medicine practice parameters define fever in the intensive care unit (ICU) as a temperature greater than 38.3°C (101°F) (8). Although this definition is not conditional on an anatomic site of temperature measurement, measurement of core temperature is recommended using an intravascular or bladder thermistor, electronic probe in the rectum or the external auditory canal (8).

Physiologically, fever is one component of the febrile response: a complex physiologic reaction to inflammation or infection involving a cytokine mediated rise in core temperature, generation of acute-phase reactants, and activation of numerous physiologic, endocrinologic and immunologic systems (9). Fever is an adaptive process where the normal body temperature is set at a higher level in response to circulating pyrogens (1-4,9). This is distinct from hyperthermic states in which temperature may rise to greater than 40°C (104 °F) (1,10). In hyperthermic states the body is unable to control core body temperature (10). Consequently, these states should be considered as a separate clinical entity requiring different evaluation and management and will not be considered in this discussion.

Fever is part of the adaptive febrile response that is triggered by tissue injury or infection. In-vitro, temperature elevation has been shown to enhance antibody production, T-cell activation, production of cytokines and enhanced neutrophil and macrophage function (1). Mammalian models have shown enhanced resistance to infection by increasing body temperature. However, in interpreting these data it is important to consider that temperature elevation *per se* cannot mimic the effects of fever because fever is just one component of the milieu of reactions taking place in the body that are triggered by inflammation or infection (9). More convincing evidence comes from experimental models of infection (not just elevated temperature) in reptiles or fish. There is a direct correlation between increased body temperature and survival and an increase in mortality if the febrile response is suppressed with sodium salicylate (9). Marik noted three studies that provide clinical evidence that fever is beneficial (1). In a retrospective analysis of 218 patients with Gram-negative bacteremia, a positive correlation was found between maximum temperature on the day of bacteremia and survival. A temperature greater than 38°C was associated with increased survival in patients with spontaneous bacterial peritonitis. In children with chickenpox, treatment with acetaminophen was associated with a longer time to crusting of lesions compared to placebo. Viewed in the context of the physiologic role of fever, these clinical observations support the concept that fever may be beneficial. Conversely, interventions

to lower body temperature may have detrimental effects.

Others have summarized the potential benefits of treating fever (1-4,9). These include symptomatic relief and the avoidance of increased oxygen demand imposed by the elevated temperature. With respect to symptomatic relief, it is often not clear exactly which symptoms are being treated and to what extent antipyresis makes the patient feel better (3). An elevated temperature may be well tolerated if it accords with the thermal set point. Profuse diaphoresis brought on by antipyretics may cause even greater discomfort (3). Nevertheless if fever is associated with symptoms that could prolong ICU stay (e.g. delirium), a therapeutic trial of antipyresis would seem reasonable. Fever increases oxygen demand, cardiac output, sympathetic tone, respiratory minute volume, and energy expenditure, all of which peak during shivering (1). Therefore it is reasonable to treat fever, provided shivering is not induced, in patients with a limited cardiorespiratory reserve or in those patients in whom fever is suspected to be causing a metabolic or cardiorespiratory deficit (1-4).

In many ICU's, treating a fever above 38.3°C (101°F) with acetaminophen is almost an automatic reaction. However, this practice could be detrimental for two reasons. First, fever has beneficial aspects as outlined above. Second, acetaminophen, like any drug, is associated with potential adverse effects. Perhaps particularly relevant with respect to even periodic dosing is the observed association between acetaminophen and hypotension in critically-ill patients. There are many causes of hypotension in the ICU such as volume depletion, cytokine-related vasodilation, cardiogenic shock, medications, increased intrathoracic pressure secondary to ventilator setting changes and secondary to a cardiac arrhythmia. Recognition of acetaminophen as a possible contributor to hypotension is important for proper assessment and treatment of hypotension in these patients.

Case Report

A 38 year old man was previously healthy until 8 days prior to hospital admission was admitted for investigation of shortness of breath, left pleuritic chest pain, fever, chills and myalgias. He was on no medications and had no known allergies. On the medical ward he received 5 doses of enteric coated ASA 325 mg for pleuritic pain then received two doses of acetaminophen 650mg for analgesia. He also received a single 2 g intravenous (IV) dose of ceftriaxone. The patient became increasingly short of breath, tachypneic and diaphoretic and was intubated within 24 hours of admission for hypoxic hypercarbic respiratory failure and admitted to the ICU.

On the first day of ICU admission, the patient was ventilated. Pulmonary embolism was ruled out by CT scan and the presumptive diagnosis was community-acquired pneumonia. The patient was started on erythromycin 1g IV and imipenem 500 mg IV each every six hours and dopamine at 2 mcg/kg/min to maintain the mean arterial pressure (MAP) at 70 mmHg.

Acetaminophen 650mg was given NG for oral temperature 39.3°C (CVP 16 cm H₂O, MAP 70 mmHg). Within 5 minutes his MAP fell to 66 mmHg and dopamine was increased to 5.9 mcg/kg/min to try to maintain MAP at 70 mmHg but the MAP continued to fall to 64 mmHg resulting in the dopamine infusion rate to be increased over next 30 minutes to 11.9 mcg/kg/min. He received pentaspan 500ml which resulted in an increase in MAP to 70 mmHg 60 minutes after the acetaminophen dose. Six hours later the patient received acetaminophen 650 mg by nasogastric (NG) tube for an oral temperature 39.6°C while dopamine was infusing at 7.1 mcg/kg/min to maintain MAP 70 mmHg. Within 10 minutes dopamine was increased to 10.1 mcg/kg/min to maintain MAP at 70 mmHg; he was given 500 ml human serum albumin, and was noted to be diaphoretic and bronchospastic with a temperature of 38.8°C 30 minutes following administration of acetaminophen. Due to tachycardia of 110-120 beats per minute (bpm), dopamine was changed to norepinephrine at 10.7 mcg/min and heart rate returned to 100 bpm baseline. Neither of these episodes of hypotension was associated with any changes on the ventilator or other drug regimens.

On day two in the ICU the ventilator parameters remained the same and a rectal dose of acetaminophen 650 mg was administered for a temperature 39.5°C. Within 30 minutes of acetaminophen administration, norepinephrine increased from 8.5 to 16 mcg/min to maintain MAP at 70 mmHg and 500 ml of pentaspan was administered. Rocuronium 50 mg IV, morphine 3 mg IV and midazolam 3 mg IV were also given 10 minutes prior to the pentaspan for assisting the ventilator. Over the rest of the day norepinephrine infusion rate was steadily increased to 33.3 mcg/min to maintain MAP of 75 mmHg.

On ICU day three, the ventilator parameters remained unchanged and norepinephrine was increased to 36.3 mcg/min to keep the MAP at 80 mmHg for decreasing urine output. With norepinephrine at 37.3 mcg/min, acetaminophen 650 mg was given NG for pyrexia and norepinephrine dose again required an increase to 49.2 mcg/min for reduction in MAP to 64 mmHg. Morphine and midazolam infusion rates remained unchanged throughout at 5 mg/hour each. No other adjustment in medications or ventilator settings were made.

On ICU day four vasopressin was started at an infusion rate of 0.02 units/min and norepinephrine requirements increased to 64 mcg/min. Pentaspan 250 ml was given,

hydrocortisone 100 mg IV every eight hours was started and vasopressin and norepinephrine were titrated up to 0.04 units/min and 70.4 mcg/min, respectively. Because of plateau pressures greater than 35cm H₂O with FiO₂ 60% the patient was changed to pressure control ventilation with PEEP at 12 cm H₂O and morphine and midazolam infusions were increased to 16 mg/hour each to suppress the drive to breathe. A cooling blanket was applied for temperature of 41.8°C and two doses of rocuronium 50 mg were given for shivering. Hydrocortisone therapy was initiated. Over the next 9 hours norepinephrine requirements decreased to 5.3 mcg/min and temperature fell to 37.2°C. On ICU day five, vasopressin was discontinued within 10 hours. The patient was discharged from ICU after a 17-day stay with a presumed diagnosis of viral illness complicated by pneumonia, acute tubular necrosis and severe peripheral neuropathy.

The hypotension associated with acetaminophen in this patient paralleled the acute phase of his septic shock and his pyrexial state. This hypotension was not reproducible on day four when his vasopressor requirements were decreasing.

Discussion

This case report illustrates the possible association between acetaminophen and hypotension. Several alternative explanations exist as well. The dramatic reduction in vasopressor requirements from day 4-5 was attributed to starting hydrocortisone and it is possible that it is the temperature *per se* and not the direct effect of the drug administration that was the cause of the hypotension. The early onset of hypotension further indicates that acetaminophen is not the cause and that the fever itself may be the cause. However, this patient did experience fever spikes that were not associated with hypotension and received doses of acetaminophen that did not appear to lead to hypotension. Although the patient was receiving large doses of furosemide, episodes of hypotension did not appear to be associated with diuresis or changes in ventilator parameters, heart rate or rhythm. The increasing MAP goals may confound the observed increased requirements of norepinephrine. Also the increased and decreased requirements of vasopressors at least in part could reflect the natural time course of septic shock. Nevertheless, there remains a possibility that hypotension could be due to acetaminophen in this case.

Although hypotension has been reported as a manifestation of anaphylaxis to acetaminophen, the first report of isolated hypotension following acetaminophen administration was in 1996 by Brown where hypotensive reactions associated with the administration of acetaminophen elixir in two patients while in the ICU were described

(5). In the first patient acetaminophen was given for analgesia while the patient was treated for hypoxemic respiratory failure and an erythematous rash. The dose and duration of acetaminophen therapy were not provided. Raw data on the time interval between dose administration and changes in MAP and vasopressor requirements were also not provided but were presented graphically. Unfortunately it is difficult to discern a clear relationship between acetaminophen administration and development of hypotension in this case because of the variation in MAP. Mean arterial pressure fluctuations around 13 doses of acetaminophen were presented as well as rates of norepinephrine, epinephrine and dopamine infusion. However, the author interpreted these data to reflect reproducible hypotension following acetaminophen. The authors ruled out other causes of hypotension such as a continuous infusion of pancuronium and dehydration. After stopping the acetaminophen no further hypotensive episodes were noted. Because of the concomitant rash, it is possible that this patient's hypotension could have been part of an undiagnosed anaphylactic reaction.

In the second case a 21 year old man admitted to the ICU with respiratory failure following consolidative chemotherapy for myeloblastic leukemia. Acetaminophen was administered enterally (exact dose not provided) to reduce oxygen demand during neutropenic fever. Mean arterial pressure fell by as much as 20 mmHg within 2 hours of acetaminophen administration. Eight doses of acetaminophen were administered over 126 hours and vasopressors were given from hours 10-20 only. The effect on temperature was not reported and doses and duration of therapy with acetaminophen were not provided. The authors ruled out hypotension due to diuresis, changes in rates of morphine or lorazepam infusions or septic shock.

After observing an apparent temporal association between acetaminophen administration and the development of hypotension in several of their ICU patients, Boyle and co-workers conducted a prospective observational cohort study in 37 patients to examine this potential relationship (7). The study population consisted of all patients given acetaminophen for the treatment of fever or pain. Systolic, diastolic and MAP were recorded 30 minutes prior to acetaminophen administration, at the time of administration and then at 15 minute intervals for the first hour and at half-hour intervals for the second hour following administration. Any requirements for fluid administration, commencement or increase rates of inotropic or vasoactive drug infusions in the 120 minute observation period following acetaminophen administration were noted. Ten patients were excluded from the final analysis; three for administration of antihypertensive medications in the hour preceding acetaminophen and seven because acetaminophen was administered rectally. The remaining 27 subjects were included in the final analysis. In 23 of the evaluable patients acetaminophen 1 gram was given to

treat fever. Although it was not stated whether any patient was in septic shock, 12 patients were receiving vasoactive infusions while seven were receiving regular anti-hypertensive medications. The changes in systolic blood pressure (SBP) were significant at all observation times after acetaminophen administration and at 30, 45, 60 and 90 minutes for the MAP; mean SBP fell from 133 ± 4.7 mmHg at -30 min to 116 ± 3.8 mmHg at 45 minutes. A maximum individual fall in SBP was by 36% at 30 minutes. Mean arterial pressure fell by 7% from baseline ($p < 0.0001$) from a mean MAP of 84 ± 2.9 mmHg at -30 min to 78 ± 2.5 mmHg at 45 min with a maximum individual fall of 34% occurring in the 30 and 45 minute study periods. No changes in ventilator settings or cardiac rhythm occurred during the study period. Fluid and vasopressor therapy was required in 29.6% of patients. Individual hemodynamic data, suspected sources of fever and effects on temperature were not reported. The authors note that due to the need to prevent reduction in MAP, treatment with fluids or vasoactive drugs were instituted. Therefore the full magnitude of the effect of acetaminophen on reduction in SBP and MAP is likely masked. It was not reported whether the patients were re-challenged with acetaminophen to assess reproducibility. Causality is difficult to ascribe to acetaminophen as individual hemodynamic data is not provided. It remains a possibility that, as in our case report, the hypotension observed may be due to cytokine release around a fever spike and not the acetaminophen *per se*.

Mackenzie et al. carried out a retrospective review of charts of all patients admitted to their ICU for instances of acetaminophen administration over a 14 month period which was recently published in abstract only (11). One-hundred-and-eighty-three episodes of acetaminophen administration in 53 patients were analyzed. Each patient served as their own control. Results indicated that MAP fell significantly from baseline at 1, 2 and 3 hours following acetaminophen administration ($p < 0.001$). As this report is only in abstract form, limited data is available. The mean fall in MAP $\pm$ SD is not provided nor were important details regarding this study such as detailed patient demographics, the indication for acetaminophen use and other potential causes of hypotension.

Association vs. Causation

Although these observational reports have limitations they are at least hypothesis-generating. Of course, association does not imply causation. It is possible that the hypotension observed in some patients receiving acetaminophen is due to the underlying fever and is unrelated to acetaminophen use. Theoretically, hypotension could also be the result of an interaction between the drug and high temperature, an interaction not observed when the drug is given to euthermic or patients with mild to moderate

temperature. It is also possible that a patient is more at risk of acetaminophen-related hypotension if they are in a certain phase of septic shock or systemic inflammatory response syndrome. In the absence of a randomized, placebo-controlled trial we would require three further pieces of evidence to support the hypothesis that acetaminophen causes hypotension. First, we would require further reports to suggest that hypotension is a consistent finding. Second, the association would be strengthened if in a given patient hypotension was not observed with onset of the febrile episode but only when acetaminophen was given to treat a separate febrile episode. These findings by themselves do not rule out that hypotension is a result of a reaction to the excipients of the formulation as considered by Brown (5). Third, assuming that it is a direct effect of acetaminophen, we require biologic plausibility: what is the mechanism of this adverse effect? Is it host and time dependent? That is, is the risk of hypotension higher when a patient is in a certain phase of their septic inflammatory response syndrome or sepsis? In the case report by Brown, and our report the patients had received acetaminophen prior to the ICU admission without documented hypotension. Also, it is unknown whether the risk of hypotension would be equally likely if aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) were given. Experimental evidence that antipyretics work by inhibiting centrally acting prostaglandin E₂ is equivocal (4). Inquiry into the underlying mechanism may further reveal the physiology of fever and the mechanism of acetaminophen's antipyretic action. Although acetaminophen is known to block IL-1, this should oppose vasodilation as IL-1 is a vasodilator. Perhaps there is a link between generation of nitric oxide by acetaminophen, such speculation may require further consideration. Although acetaminophen-related hypotension could be part of a delayed hypersensitivity reaction, other concomitant symptoms such as skin rash and eosinophilia were not present in our patient. Although the patient in our case report was bronchospastic this could be attributed to pulmonary edema.

Conclusion

Fever is part of the febrile response to inflammation or infection which is an adaptive process with physiologic benefit. With the known physiologic benefits of fever and potential adverse effects of treatment it should no longer be routine practice to treat fever (1-4). Antipyretics should be initiated as a therapeutic trial only if there is clinical evidence of, or risk for metabolic or cardiorespiratory compromise, or if the fever may be causing symptoms that could prolong ICU stay (e.g. delirium). Ideally, the initiation of a therapeutic trial with acetaminophen should be done without co-intervention so that any observed benefit can be attributed to antipyresis. Whatever the indication, evidence of benefit should be established for treatment to be continued. In the critically ill,

acetaminophen administration may be associated with hypotension. Therefore, clinicians should be vigilant for and report hypotensive episodes that may follow administration of acetaminophen and possibly aspirin or other NSAIDs.

Acknowledgement

I would like to acknowledge the expert observations of Susanne Yard, RN, who identified the temporal association of acetaminophen administration with hypotension in this case.

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Hypotension Associated with Acetaminophen Administration in the Critically-ill: Another Reason Not to Treat a Fever?

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Fever is part of the febrile response to inflammation or infection which is an adaptive process with physiologic benefit. Although antipyretics are frequently administered to treat fever in the critically ill some clinicians have advocated against this routine practice and advocate for a careful evaluation of the risks and benefits of treating a fever to established need in each case. In light of recent reports of hypotension following acetaminophen administration, the argument against treating a fever in the critically ill may have further justification. This paper describes a case of possible acetaminophen-induced hypotension in a critically-ill patient and discusses the potential association between this relationship.

J Inform Pharmacother 2001;5:300-305.

Although antipyretics are frequently administered to treat fever in the critically ill, many authors have advocated against this routine practice (1-4). Instead, they argue, a careful evaluation of the risks and benefits of treating a fever should be established in each case. In light of recent reports of hypotension following acetaminophen administration, the argument against treating a fever in the critically ill may have further justification (5-7).

The thermometric definition of fever is arbitrary and depends upon the purpose for which it is defined. For the purpose of warranting diagnostic investigation, the Society of Critical Care Medicine practice parameters define fever in the intensive care unit (ICU) as a temperature greater than 38.3°C (101°F) (8). Although this definition is not conditional on an anatomic site of temperature measurement, measurement of core temperature is recommended using an intravascular or bladder thermistor, electronic probe in the rectum or the external auditory canal (8).

Physiologically, fever is one component of the febrile response: a complex physiologic reaction to inflammation or infection involving a cytokine mediated rise in core temperature, generation of acute-phase reactants, and activation of numerous physiologic, endocrinologic and immunologic systems (9). Fever is an adaptive process where the normal body temperature is set at a higher level in response to circulating pyrogens (1-4,9). This is distinct from hyperthermic states in which temperature may rise to greater than 40°C (104 °F) (1,10). In hyperthermic states the body is unable to control core body temperature (10). Consequently, these states should be considered as a separate clinical entity requiring different evaluation and management and will not be considered in this discussion.

Fever is part of the adaptive febrile response that is triggered by tissue injury or infection. In-vitro, temperature elevation has been shown to enhance antibody production, T-cell activation, production of cytokines and enhanced neutrophil and macrophage function (1). Mammalian models have shown enhanced resistance to infection by increasing body temperature. However, in interpreting these data it is important to consider that temperature elevation *per se* cannot mimic the effects of fever because fever is just one component of the milieu of reactions taking place in the body that are triggered by inflammation or infection (9). More convincing evidence comes from experimental models of infection (not just elevated temperature) in reptiles or fish. There is a direct correlation between increased body temperature and survival and an increase in mortality if the febrile response is suppressed with sodium salicylate (9). Marik noted three studies that provide clinical evidence that fever is beneficial (1). In a retrospective analysis of 218 patients with Gram-negative bacteremia, a positive correlation was found between maximum temperature on the day of bacteremia and survival. A temperature

greater than 38°C was associated with increased survival in patients with spontaneous bacterial peritonitis. In children with chickenpox, treatment with acetaminophen was associated with a longer time to crusting of lesions compared to placebo. Viewed in the context of the physiologic role of fever, these clinical observations support the concept that fever may be beneficial. Conversely, interventions to lower body temperature may have detrimental effects.

Others have summarized the potential benefits of treating fever (1-4,9). These include symptomatic relief and the avoidance of increased oxygen demand imposed by the elevated temperature. With respect to symptomatic relief, it is often not clear exactly which symptoms are being treated and to what extent antipyresis makes the patient feel better (3). An elevated temperature may be well tolerated if it accords with the thermal set point. Profuse diaphoresis brought on by antipyretics may cause even greater discomfort (3). Nevertheless if fever is associated with symptoms that could prolong ICU stay (e.g. delirium), a therapeutic trial of antipyresis would seem reasonable. Fever increases oxygen demand, cardiac output, sympathetic tone, respiratory minute volume, and energy expenditure, all of which peak during shivering (1). Therefore it is reasonable to treat fever, provided shivering is not induced, in patients with a limited cardiorespiratory reserve or in those patients in whom fever is suspected to be causing a metabolic or cardiorespiratory deficit (1-4).

In many ICU's, treating a fever above 38.3°C (101°F) with acetaminophen is almost an automatic reaction. However, this practice could be detrimental for two reasons. First, fever has beneficial aspects as outlined above. Second, acetaminophen, like any drug, is associated with potential adverse effects. Perhaps particularly relevant with respect to even periodic dosing is the observed association between acetaminophen and hypotension in critically-ill patients. There are many causes of hypotension in the ICU such as volume depletion, cytokine-related vasodilation, cardiogenic shock, medications, increased intrathoracic pressure secondary to ventilator setting changes and secondary to a cardiac arrhythmia. Recognition of acetaminophen as a possible contributor to hypotension is important for

proper assessment and treatment of hypotension in these patients.

Case Report

A 38 year old man was previously healthy until 8 days prior to hospital admission was admitted for investigation of shortness of breath, left pleuritic chest pain, fever, chills and myalgias. He was on no medications and had no known allergies. On the medical ward he received 5 doses of enteric coated ASA 325 mg for pleuritic pain then received two doses of acetaminophen 650mg for analgesia. He also received a single 2 g intravenous (IV) dose of ceftriaxone. The patient became increasingly short of breath, tachypneic and diaphoretic and was intubated within 24 hours of admission for hypoxic hypercarbic respiratory failure and admitted to the ICU.

On the first day of ICU admission, the patient was ventilated. Pulmonary embolism was ruled out by CT scan and the presumptive diagnosis was community-acquired pneumonia. The patient was started on erythromycin 1g IV and imipenem 500 mg IV each every six hours and dopamine at 2 mcg/kg/min to maintain the mean arterial pressure (MAP) at 70 mmHg.

Acetaminophen 650mg was given NG for oral temperature 39.3°C (CVP 16 cm H₂O, MAP 70 mmHg). Within 5 minutes his MAP fell to 66 mmHg and dopamine was increased to 5.9 mcg/kg/min to try to maintain MAP at 70 mmHg but the MAP continued to fall to 64 mmHg resulting in the dopamine infusion rate to be increased over next 30 minutes to 11.9 mcg/kg/min. He received pentaspan 500ml which resulted in an increase in MAP to 70 mmHg 60 minutes after the acetaminophen dose. Six hours later the patient received acetaminophen 650 mg by nasogastric (NG) tube for an oral temperature 39.6°C while dopamine was infusing at 7.1 mcg/kg/min to maintain MAP 70 mmHg. Within 10 minutes dopamine was increased to 10.1 mcg/kg/min to maintain MAP at 70 mmHg; he was given 500 ml human serum albumin, and was noted to be diaphoretic and bronchospastic with a temperature of 38.8°C 30 minutes following administration of acetaminophen. Due to tachycardia of 110-120 beats per minute (bpm), dopamine was changed to norepinephrine at 10.7 mcg/min and heart rate returned to 100 bpm baseline. Neither of these

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episodes of hypotension was associated with any changes on the ventilator or other drug regimens.

On day two in the ICU the ventilator parameters remained the same and a rectal dose of acetaminophen 650 mg was administered for a temperature 39.5°C. Within 30 minutes of acetaminophen administration, norepinephrine increased from 8.5 to 16 mcg/min to maintain MAP at 70 mmHg and 500 ml of pentaspan was administered. Rocuronium 50 mg IV, morphine 3 mg IV and midazolam 3 mg IV were also given 10 minutes prior to the pentaspan for assisting the ventilator. Over the rest of the day norepinephrine infusion rate was steadily increased to 33.3 mcg/min to maintain MAP of 75 mmHg.

On ICU day three, the ventilator parameters remained unchanged and norepinephrine was increased to 36.3 mcg/min to keep the MAP at 80 mmHg for decreasing urine output. With norepinephrine at 37.3 mcg/min, acetaminophen 650 mg was given NG for pyrexia and norepinephrine dose again required an increase to 49.2 mcg/min for reduction in MAP to 64 mmHg. Morphine and midazolam infusion rates remained unchanged throughout at 5 mg/hour each. No other adjustment in medications or ventilator settings were made.

On ICU day four vasopressin was started at an infusion rate of 0.02 units/min and norepinephrine requirements increased to 64 mcg/min. Pentaspan 250 ml was given, hydrocortisone 100 mg IV every eight hours was started and vasopressin and norepinephrine were titrated up to 0.04 units/min and 70.4 mcg/min, respectively. Because of plateau pressures greater than 35cm H₂O with FiO₂ 60% the patient was changed to pressure control ventilation with PEEP at 12 cm H₂O and morphine and midazolam infusions were increased to 16 mg/hour each to suppress the drive to breathe. A cooling blanket was applied for temperature of 41.8°C and two doses of rocuronium 50 mg were given for shivering. Hydrocortisone therapy was initiated. Over the next 9 hours norepinephrine requirements decreased to 5.3 mcg/min and temperature fell to 37.2°C. On ICU day five, vasopressin was discontinued within 10 hours. The patient was discharged from ICU after a 17-day stay with a presumed diagnosis of viral illness

complicated by pneumonia, acute tubular necrosis and severe peripheral neuropathy.

The hypotension associated with acetaminophen in this patient paralleled the acute phase of his septic shock and his pyrexial state. This hypotension was not reproducible on day four when his vasopressor requirements were decreasing.

Discussion

This case report illustrates the possible association between acetaminophen and hypotension. Several alternative explanations exist as well. The dramatic reduction in vasopressor requirements from day 4-5 was attributed to starting hydrocortisone and it is possible that it is the temperature *per se* and not the direct effect of the drug administration that was the cause of the hypotension. The early onset of hypotension further indicates that acetaminophen is not the cause and that the fever itself may be the cause. However, this patient did experience fever spikes that were not associated with hypotension and received doses of acetaminophen that did not appear to lead to hypotension. Although the patient was receiving large doses of furosemide, episodes of hypotension did not appear to be associated with diuresis or changes in ventilator parameters, heart rate or rhythm. The increasing MAP goals may confound the observed increased requirements of norepinephrine. Also the increased and decreased requirements of vasopressors at least in part could reflect the natural time course of septic shock. Nevertheless, there remains a possibility that hypotension could be due to acetaminophen in this case.

Although hypotension has been reported as a manifestation of anaphylaxis to acetaminophen, the first report of isolated hypotension following acetaminophen administration was in 1996 by Brown where hypotensive reactions associated with the administration of acetaminophen elixir in two patients while in the ICU were described (5). In the first patient acetaminophen was given for analgesia while the patient was treated for hypoxemic respiratory failure and an erythematous rash. The dose and duration of acetaminophen therapy were not provided. Raw data on the time interval between dose administration and changes in MAP and

vasopressor requirements were also not provided but were presented graphically. Unfortunately it is difficult to discern a clear relationship between acetaminophen administration and development of hypotension in this case because of the variation in MAP. Mean arterial pressure fluctuations around 13 doses of acetaminophen were presented as well as rates of norepinephrine, epinephrine and dopamine infusion. However, the author interpreted these data to reflect reproducible hypotension following acetaminophen. The authors ruled out other causes of hypotension such as a continuous infusion of pancuronium and dehydration. After stopping the acetaminophen no further hypotensive episodes were noted. Because of the concomitant rash, it is possible that this patient's hypotension could have been part of an undiagnosed anaphylactic reaction.

In the second case a 21 year old man admitted to the ICU with respiratory failure following consolidative chemotherapy for myeloblastic leukemia. Acetaminophen was administered enterally (exact dose not provided) to reduce oxygen demand during neutropenic fever. Mean arterial pressure fell by as much as 20 mmHg within 2 hours of acetaminophen administration. Eight doses of acetaminophen were administered over 126 hours and vasopressors were given from hours 10-20 only. The effect on temperature was not reported and doses and duration of therapy with acetaminophen were not provided. The authors ruled out hypotension due to diuresis, changes in rates of morphine or lorazepam infusions or septic shock.

After observing an apparent temporal association between acetaminophen administration and the development of hypotension in several of their ICU patients, Boyle and co-workers conducted a prospective observational cohort study in 37 patients to examine this potential relationship (7). The study population consisted of all patients given acetaminophen for the treatment of fever or pain. Systolic, diastolic and MAP were recorded 30 minutes prior to acetaminophen administration, at the time of administration and then at 15 minute intervals for the first hour and at half-hour intervals for the second hour following administration. Any requirements for fluid administration, commencement or increase rates of inotropic or vasoactive drug infusions in the 120 minute observation period following acetaminophen administration were noted. Ten patients were

excluded from the final analysis; three for administration of antihypertensive medications in the hour preceding acetaminophen and seven because acetaminophen was administered rectally. The remaining 27 subjects were included in the final analysis. In 23 of the evaluable patients acetaminophen 1 gram was given to treat fever. Although it was not stated whether any patient was in septic shock, 12 patients were receiving vasoactive infusions while seven were receiving regular antihypertensive medications. The changes in systolic blood pressure (SBP) were significant at all observation times after acetaminophen administration and at 30, 45, 60 and 90 minutes for the MAP; mean SBP fell from 133 ± 4.7 mmHg at -30 min to 116 ± 3.8 mmHg at 45 minutes. A maximum individual fall in SBP was by 36% at 30 minutes. Mean arterial pressure fell by 7% from baseline ($p < 0.0001$) from a mean MAP of 84 ± 2.9 mmHg at -30 min to 78 ± 2.5 mmHg at 45 min with a maximum individual fall of 34% occurring in the 30 and 45 minute study periods. No changes in ventilator settings or cardiac rhythm occurred during the study period. Fluid and vasopressor therapy was required in 29.6% of patients. Individual hemodynamic data, suspected sources of fever and effects on temperature were not reported. The authors note that due to the need to prevent reduction in MAP, treatment with fluids or vasoactive drugs were instituted. Therefore the full magnitude of the effect of acetaminophen on reduction in SBP and MAP is likely masked. It was not reported whether the patients were re-challenged with acetaminophen to assess reproducibility. Causality is difficult to ascribe to acetaminophen as individual hemodynamic data is not provided. It remains a possibility that, as in our case report, the hypotension observed may be due to cytokine release around a fever spike and not the acetaminophen *per se*.

Mackenzie et al. carried out a retrospective review of charts of all patients admitted to their ICU for instances of acetaminophen administration over a 14 month period which was recently published in abstract only (11). One-hundred-and-eighty-three episodes of acetaminophen administration in 53 patients were analyzed. Each patient served as their own control. Results indicated that MAP fell significantly from baseline at 1, 2 and 3 hours following acetaminophen administration ($p < 0.001$). As this report is only in abstract form, limited data is available. The mean fall in MAP $\pm$ SD is not provided nor were important

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details regarding this study such as detailed patient demographics, the indication for acetaminophen use and other potential causes of hypotension.

Association vs. Causation

Although these observational reports have limitations they are at least hypothesis-generating. Of course, association does not imply causation. It is possible that the hypotension observed in some patients receiving acetaminophen is due to the underlying fever and is unrelated to acetaminophen use. Theoretically, hypotension could also be the result of an interaction between the drug and high temperature, an interaction not observed when the drug is given to euthermic or patients with mild to moderate temperature. It is also possible that a patient is more at risk of acetaminophen-related hypotension if they are in a certain phase of septic shock or systemic inflammatory response syndrome. In the absence of a randomized, placebo-controlled trial we would require three further pieces of evidence to support the hypothesis that acetaminophen causes hypotension. First, we would require further reports to suggest that hypotension is a consistent finding. Second, the association would be strengthened if in a given patient hypotension was not observed with onset of the febrile episode but only when acetaminophen was given to treat a separate febrile episode. These findings by themselves do not rule out that hypotension is a result of a reaction to the excipients of the formulation as considered by Brown (5). Third, assuming that it is a direct effect of acetaminophen, we require biologic plausibility: what is the mechanism of this adverse effect? Is it host and time dependent? That is, is the risk of hypotension higher when a patient is in a certain phase of their septic inflammatory response syndrome or sepsis? In the case report by Brown, and our report the patients had received acetaminophen prior to the ICU admission without documented hypotension. Also, it is unknown whether the risk of hypotension would be equally likely if aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) were given. Experimental evidence that antipyretics work by inhibiting centrally acting prostaglandin E_2 is equivocal (4). Inquiry into the underlying mechanism may further reveal the physiology of fever and the mechanism of acetaminophen's antipyretic action. Although acetaminophen is known to block IL-1, this

should oppose vasodilation as IL-1 is a vasodilator. Perhaps there is a link between generation of nitric oxide by acetaminophen, such speculation may require further consideration. Although acetaminophen-related hypotension could be part of a delayed hypersensitivity reaction, other concomitant symptoms such as skin rash and eosinophilia were not present in our patient. Although the patient in our case report was bronchospastic this could be attributed to pulmonary edema.

Conclusion

Fever is part of the febrile response to inflammation or infection which is an adaptive process with physiologic benefit. With the known physiologic benefits of fever and potential adverse effects of treatment it should no longer be routine practice to treat fever (1-4). Antipyretics should be initiated as a therapeutic trial only if there is clinical evidence of, or risk for metabolic or cardiorespiratory compromise, or if the fever may be causing symptoms that could prolong ICU stay (e.g. delirium). Ideally, the initiation of a therapeutic trial with acetaminophen should be done without co-intervention so that any observed benefit can be attributed to antipyresis. Whatever the indication, evidence of benefit should be established for treatment to be continued. In the critically ill, acetaminophen administration may be associated with hypotension. Therefore, clinicians should be vigilant for and report hypotensive episodes that may follow administration of acetaminophen and possibly aspirin or other NSAIDs.

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Pharmacotherapy on the Web

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Do Bugs Need Drugs?, HandHeldMed Mobile Abstracts, Allied Journal Club, CDC Hoaxes and Rumors Site, Ontario Program for Optimal Therapeutics

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JIP Site Evaluation Process

Do Bugs Need Drugs?, HandHeldMed Mobile Abstracts, Allied Journal Club, CDC Hoaxes and Rumors Site, Ontario Program for Optimal Therapeutics

Name of site:	Do Bugs Need Drugs?
Type of site:	Information about antibiotics, treatment and resistance.
Authoring organization:	Capital Health Region (Edmonton, Alberta), Alberta Clinical Practice Guidelines, University of Alberta, Alberta Lung Association
Sponsors:	IMS Health, Videon, Abbott Laboratories, Dynacare Kasper Medical Laboratories, Aventis, Bayer, Bristol-Myers Squibb, Deb Canada, GlaxoWellcome, Janssen-Ortho Inc., Pfizer Canada Inc., SmithKline Beecham, bioMerieux, Glo Germ, Mistahia Health Region, Health Canada, Yellowhead Tribal Council
Of particular interest to:	Healthcare professionals, occupational health practitioners, parents, children, teachers.
Completeness Score (/5)	4.5
Credibility Score (/5)	4.5
Usability Score (/5)	5
Why is it useful? (what will it help me DO?):	For health care professionals, this site provides an alternative source of infectious disease treatment recommendations with a Canadian flavour.

Commentary: This site has all sections of "Bugs & Drugs Antimicrobial Pocket Reference 2001" available as a free download in Adobe PDF format. When you get to the antimicrobial pocket reference page URLs, don't forget to scroll down to see all the available sections offered (e.g.. empiric therapy, prophylaxis recommendations, pregnancy/lactation...), as not everything you need are available in the "Clinical Antibiotic Guidelines".

Also a great resource for parents, teachers and children to learn about the basics of handwashing, resistance and common infectious ailments. The site features special sections designed specifically for teachers, parents, the general public, kids, occupational health, and health care professionals.

URL of site: <http://dobugsneeddrugs.org>

Reviewed by: Anne Nguyen, PharmD

Name of site: **HandHeldMed - Mobile Abstracts**

Type of site: Journal abstracting service for mobile computers

Authoring organization: HandHeldMed.com

Sponsors: Supported through banner advertising and sales of software products.

Of particular interest to: Any health professional who owns or is considering owning a handheld computer (eg. Palm Pilot, Visor, Pocket PC)

Completeness Score 3
(/5)

Credibility Score (/5) 5

Usability Score (/5) 4

Why is it useful? (what will it help me DO?): Provides table of contents and article abstracts for major journals which can be downloaded to your Palm OS-based portable computer.

Commentary: If you are a handheld computer user, the number one reason to install and use AvantGo (available for FREE download at AvantGo.com) is the fact that you can carry the JIP with you wherever you go (see the [JIP Mobile Edition page](#)). The second best reason to run AvantGo is that HandHeldMed now provides access to the Table of Contents and article abstracts of 29 major journals which you can carry with you on your Palm or CE device. Best of all, the service is completely free. As an avid Palm user, I've been trying various ways of getting this kind of information onto my Palm so I can keep abreast of the literature while on the bus, in my car, while snowboarding or on the 15th teebox. This service makes it easier than any method I've devised. The major general medical journals are all on the list (e.g. JAMA, Ann Intern Med, Lancet, BMJ, NEJM) and they claim that "hundreds" more are on the way. I'm hoping CMAJ and Archives of Internal Med are on the way. For other subspecialties and disciplines, there are already several journals which may be of interest (eg. Nursing Outlook, American Journal of Epidemiology).

The Journals run as individual "channels" in AvantGo and most occupy less than 50kb each in memory. The AvantGo application itself consumes about 500kb of memory. It is easy to delete the channels once installed, and adding new ones requires a visit to the HandHeldMed.com site.

Although HandHeldMed.com was featured in Issue 4 of the JIP, I think this new service is an excellent reason to pay them another visit... and download AvantGo.

URL of site: <http://www.handheldmed.com/mobilecontent.php>

Reviewed by: Peter Loewen, Pharm.D.

Name of site: **Allied Journal Club**

Type of site: Journal surveillance site.

Authoring organization: Muhammad Zuberi, a Toronto pharmacist

Sponsors: None named.

Of particular interest to: Any health care professional seeking quick access to journal abstracts or current literature on specific therapeutics topics.

Completeness Score 4
(/5)

Credibility Score (/5) 5

Usability Score (/5) 3

Why is it useful? (what will it help me DO?): Provides a quick way of locating the contents of specific journals without visiting each journal's site. Also facilitates quick PubMed searches on specific therapeutics topics.

Commentary: More than anything, this site is a clever way to search the National Library of Medicine's PubMed database. Muhammad Zuberi's site, which is obviously a labor of love, allows users to view the citations from 25 individual journals (including Pharmacotherapy and Annals of Pharmacotherapy) by issue or search across 150 journals for articles on selected therapeutics topics. The site contains no content of its own, but provides a simple and quick (but limited) interface for accessing PubMed. Since the author is a pharmacist, the topics are nicely suited to issues germane to drug therapy. Users can also subscribe to receive free e-mail updates from as many journals as they wish.

This site recently won Honorable Mention in Pharmacy Practice's 2000 Commitment to Care Awards for Hospital Pharmacy.

URL of site: <http://www.alliedjournalclub.com>

Reviewed by: Peter Loewen, Pharm.D.

Name of site:	Centers for Disease Control & Prevention Hoaxes and Rumors Site
Type of site:	Information about current health-related hoaxes and rumors.
Authoring organization:	U.S. Centers for Disease Control & Prevention
Sponsors:	CDC
Of particular interest to:	Pharmacotherapy practitioners and physicians interested in the pharmaceutical industry's influences on health care.
Completeness Score (/5)	2 (not intended to be a comprehensive site)
Credibility Score (/5)	5
Usability Score (/5)	5
Why is it useful? (what will it help me DO?):	Prevent perpetuating false health-related stories on rounds or in the cafeteria.
Commentary:	In keeping with the traditions set by urbanlegends.com, QuackWatch and computer virus hoax sites, the CDC has launched this informative site which takes aim at health hoaxes and rumors circulating in the lay press and on the internet (WHAT? the Internet as a source of RUMORS?). Not surprisingly, the stories the site deals with seem to be focused on infectious diseases-related issues (eg. needlestick hoaxes, transmission of HIV through the air) which have come to the CDC's attention. The next time you hear a surprising story about a disease being transmitted via fiber-optic cables, check this site.
URL of site:	http://www.cdc.gov/hoax_rumors.htm
Reviewed by:	Peter Loewen, Pharm.D.

Name of site:	Ontario Program for Optimal Therapeutics
Type of site:	Guidelines for management of common conditions.
Authoring organization:	Ontario Program for Optimal Therapeutics
Sponsors:	Ontario Ministry of Health and Long-Term Care
Of particular interest to:	Primary care physicians and pharmacists.
Completeness Score (/5)	2 (only seven guidelines published)
Credibility Score (/5)	4
Usability Score (/5)	3
Why is it useful? (what will it help me DO?):	Provides clear, mostly evidence-based guidelines for management of osteoporosis, CHF, stable ischemic heart disease, OA/RA/MSK injury, GERD, diabetes and anxiety.

Commentary: Through a process of literature review, multidisciplinary expert opinion-gathering, and consensus building, the OPOT site has published guidelines for management of seven diseases in primary care. The guidelines themselves are concise, use algorithms and tables extensively and are thoroughly references.

The relationship between this group and the Ontario government's drug benefit plan is not explicitly mentioned on the site. The process of guideline development is described and does not appear to include involvement of pharmaceutical industry representatives.

URL of site: <http://www.opot.org/>

Reviewed by: [Peter Loewen](#), Pharm.D.

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Pharmacotherapy on the Web

The Journal of Informed Pharmacotherapy 2000;1:500.

Grapefruit Juice Drug Interactions, Quackwatch, Clinical Pharmacology 2000, Pediatric Pharmacotherapy, Canadian Drug Products Database, Healthy PalmPilot, Internet FDA

JIP Site Evaluation Process

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Sites previously reviewed

Grapefruit Juice Drug Interactions, Quackwatch, Clinical Pharmacology 2000, Pediatric Pharmacotherapy, Canadian Drug Products Database , Healthy PalmPilot, Internet FDA

Name of site:	Grapefruit Juice - Drug Interactions Homepage
Type of site:	Specialized drug interaction database
Authoring organization:	Dean Elbe, B.Sc.(Pharm.)
Sponsors:	None stated.
Of particular interest to:	Pharmacotherapy practitioners and patients.
Completeness Score (/5)	4
Credibility Score (/5)	4
Usability Score (/5)	4
Why is it useful? (what will it help me DO?):	This site provides one-stop shopping for clinicians seeking information on which drugs interact with grapefruit juice as well as descriptions of the significance of the interactions. Pulling together this information from general databases could be very time-consuming for clinicians.
Commentary:	The site is kept fairly up to date and is very well referenced. Of particular use is the listing of unconfirmed but potential interactions (which may be hard to find elsewhere) and the list of confirmed LACK of interactions for certain drugs.
URL of site:	http://www.powernetdesign.com/grapefruit/
Reviewed by:	Peter Loewen, Pharm.D.

Name of site:	Health Canada Drug Product Database
Type of site:	Drug database

Authoring organization:	Health Canada
Sponsors:	Health Canada Therapeutic Products Program (Federal Government of Canada)
Of particular interest to:	Pharmacotherapy practitioners in Canada
Completeness Score (/5)	5
Credibility Score (/5)	5
Usability Score (/5)	4
Why is it useful? (what will it help me DO?):	It allows practitioners to quickly find out which products are marketed in Canada, by whom, strengths, and search by brand name, generic name, DIN, or manufacturer.
Commentary:	Health Canada keeps this site up to date, so a product will be listed in the database within days of it being marketed in Canada. The database includes all non-prescription products as well (provided they are regulated by Health Canada). For those seeking a product that contains a certain ingredient (say, in a combination product) the database allows searches by active ingredients. Useful cross-referencing is provided and many sections of the database entries are linked to other similar entries, which makes finding and choosing a product easier. Products such as herbals, which are not regulated by the TPP are not included in the database.
URL of site:	http://www.hc-sc.gc.ca/hpb/drugs-dpd/
Reviewed by:	Peter Loewen, Pharm.D.

Name of site:	Clinical Pharmacology 2000
Type of site:	Drug information database
Authoring organization:	Gold Standard Multimedia
Sponsors:	Gold Standard Multimedia
Of particular interest to:	Pharmacotherapy practitioners of all types.
Completeness Score (/5)	5
Credibility Score (/5)	4.5
Usability Score (/5)	4.5

Why is it useful? (what will it help me DO?):	Facilitates clinical decision-making by allowing quick access to a variety of databases including current, in-depth, referenced drug information, a drug interaction database, a product identification database, drug comparison tables, IV compatibility data, and adverse reactions.
Commentary:	This is truly the gold standard of drug information and prescribing information sources on the web. It has formerly been available only to paying subscribers but is now open for free access. This appears to be supported by advertising, some of which is by the pharmaceutical industry. The editors state, however, that advertisers have no input into the editorial process. Most of the editorial board is composed of Pharm.D.-trained drug information specialists. Monographs are well referenced, dated, and current. The database includes investigational drugs once they reach Phase III studies and includes selected popular herbal products. The index pane on the right works particularly well and eliminates large amounts of "back"-button use on the browser. Innovative features: Ability to create detailed patient medical records, including medication profiles on the server. When viewing a drug monograph, click on the "Rx" icon to open up the 'prescription writer' which allows prescribers to fill in fields and print a legible prescription which can be given to the patient or faxed to the pharmacist. A comprehensive list of laboratory tests including reference values. Users can even modify the results ranges to suit local needs. Overall, this site is a very valuable resource, and as long as it remains free to access, may cause some to consider abandoning expensive drug information database subscriptions.
URL of site:	http://www.gsm.com
Reviewed by:	Peter Loewen, Pharm.D.

Name of site:	Pediatric Pharmacotherapy
Type of site:	Medical information
Authoring organization:	University of Virginia Health Sciences Center: Children's Medical Center
Sponsors:	None
Of particular interest to:	Pediatric pharmacotherapy practitioners
Completeness Score (/5)	4.5
Credibility Score (/5)	4
Usability Score (/5)	4

Why is it useful? (what will it help me DO?):	Stated goals are to provide a brief, referenced, peer-reviewed source of information specifically related the to initiation and monitoring of medications in children in the primary care setting. This site will help users stay abreast of current issues in pediatric pharmacotherapy.
Commentary:	This site is an excellent source of up-to-date information for health care professionals specifically looking for pediatric pharmacotherapy topics. The items covered are often very timely, well-written and extensively researched. The main topics covered in each newsletter are often items for which it can be difficult to quickly locate reliable information (e.g. Ciprofloxacin use in children: a review of recent findings. 1998, volume 4, issue 12).
URL of site:	http://www.med.virginia.edu/cmc/pedpharm/pedpharm.html
Reviewed by:	Carlo Marra, Pharm.D.

Name of site:	Quackwatch
Type of site:	Database and discussion of dubious medical practices
Authoring organization:	Quackwatch, Inc., headed by Stephen Barrett, MD.
Sponsors:	Quackwatch, Inc. No corporate sponsors or ties of any kind.
Of particular interest to:	Pharmacotherapy practitioners and anyone with an interest in studying the validity of questionable therapies.
Completeness Score (/5)	4
Credibility Score (/5)	4.5
Usability Score (/5)	4
Why is it useful? (what will it help me DO?):	It allows quick access to a very large database of articles written by health care professionals (mainly physicians) on questionable treatments which are in demand by many patients or aggressively marketed. This allows pharmacotherapy practitioners to provide their patients with an educated opinion about therapies which are not discussed in the medical literature, but are in high demand by patients nonetheless.
Commentary:	Most of the articles are referenced as well as they can be (considering the lack of available evidence for many of the treatments). Some very useful articles about the methods used by purveyors of dubious products enable readers to hone their skills of healthy skepticism. Most of the information is very current (less than 2 years old) and is updated frequently. Where links to other resources are appropriate, they are provided. Overall, this represents the most useful database of dubious medical therapies that I am aware of on the web.
URL of site:	http://www.quackwatch.com
Reviewed by:	Peter Loewen, Pharm.D.

Name of site:	Healthy PalmPilot

Type of site:	Repository of downloadable health care resources for Palm OS devices
Authoring organization:	Eric Tam, MD (Web Master)
Sponsors:	Appears to be unaffiliated.
Of particular interest to:	Any healthcare worker who uses a Palm OS device.
Completeness Score (/5)	4.5
Credibility Score (/5)	4
Usability Score (/5)	4.5
Why is it useful? (what will it help me DO?):	This is a good site for geeks to visit on a frequent basis to determine what health-related freeware/shareware applications are available for Palm OS devices. User-based ratings are also provided.
Commentary:	The site is updated regularly. As of April 7, 2000, there are 505 resources listed for download. That should be enough applications available to make PDA believers out of the even the most skeptical.
URL of site:	http://www.healthypalmpilot.com
Reviewed by:	Peter Jewesson, PhD, FCSHP

Name of site:	Internet FDA
Type of site:	Government Agency Website
Authoring organization:	U.S. Food and Drug Administration (U.S. F.D.A)
Sponsors:	U.S. Food and Drug Administration (U.S. F.D.A)
Of particular interest to:	Anyone interested in the U.S. F.D.A.-related information regarding healthcare issues.
Completeness Score (/5)	4.5
Credibility Score (/5)	4.5
Usability Score (/5)	4
Why is it useful? (what will it help me DO?):	This site will help users access information pertaining to drug-related issues in the U.S.. This is an source of extensive U.S. F.D.A.-based information on a variety of topics including foods, human and animal drugs, medical devices, biologicals, bioengineered foods, toxicological research and many other topics.

Commentary: Check out the MedWatch section. This is the U.S. F.D.A. medical products reporting program. As described by the authors "... MedWatch, the FDA Medical Products Reporting Program, is an initiative designed both to educate all health professionals about the critical importance of being aware of, monitoring for, and reporting adverse events and problems to FDA and/or the manufacturer and; to ensure that new safety information is rapidly communicated to the medical community thereby improving patient care..."

Continuously updated and permits on line reporting as well). Very useful downloadable PDF files.

URL of site: <http://www.fda.gov>

Reviewed by: Peter Jewesson, PhD, FCSHP

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Incorrect Text

In the Evidence Based Review article entitled "Therapy for Helicobacter pylori in Patients with Nonulcer Dyspepsia: Eradicate or Not?" published in The Journal of Informed Pharmacotherapy 2001;5:207-209, an error occurred on page 208. Under Question 5, the last sentence should read "Tests for heterogeneity across studies were performed. A p value of less than **0.05** indicated statistical heterogeneity, meaning that the trials were too different to combine in a meta-analysis."

[View the Evidence Based Review Article](#)

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Journal of Informed Pharmacotherapy 2001;6 (July-Sept)

Editorial

- Generic vs. brand name drugs: The warfarIN debate is weaRing thin
James McCormack

Evidence-Based Reviews of the Pharmacotherapeutic Literature with emphasis on interpretation of the findings, designed to help practitioners put the findings into proper perspective

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**Updated
April 15, 2002**

Editorial

Generic vs. brand name drugs: The warfarIN debate is weaRing thin

The debate over within-class, brand-to-brand and brand-to-generic drug substitution has intensified with introduction of multiple brands of so-called "narrow therapeutic index drugs" such as warfarin. (1)

Canada's Therapeutic Products Directorate of the Health Protection Branch (HPB) has proposed a definition for drugs with narrow therapeutic indices:

"A drug is considered to have a narrow therapeutic index or range (NTI or NTR) when the ratio of the lowest concentration at which clinical toxicity commonly occurs, to the median concentration providing a therapeutic effect, is less than or equal to 2. An example of such a drug is theophylline [minimum toxic concentration (20 mg/L): median effective concentration (10 mg/L) = 2]. This policy also applies to drugs which do not fit this definition of NTR but which generally require therapeutic drug monitoring." (2)

I was recently asked to present a talk at a forum on narrow therapeutic index drugs and to discuss the issue of generic substitution in relation to narrow therapeutic index drugs. When I reviewed this information the following were considered to be narrow therapeutic index drugs by the HPB:

- Asthma: Aminophylline and derivatives
- Epilepsy/chronic pain: Carbamazepine, Phenytoin and derivatives, Valproic acid and derivatives, Primidone
- Antiarrhythmics: Disopyramide, Flecainide, Mexiletine, Procainamide, Quinidine, Tocainide
- Digoxin and derivatives
- Antibiotics: Clindamycin
- Antihypertensives: Clonidine, Minoxidil, Prazosin
- Psychiatric conditions: Clozapine, Lithium
- Parkinsonism: Trihexyphenidyl
- Transplant: Cyclosporin
- AIDS: Dideoxyinosine, Zidovudine
- Warfarin and derivatives

While one can clearly debate which drugs should actually be included (or excluded) from this list, the theory behind the creation of this list is that therapeutic and toxic drug concentrations are similar enough that "small" differences (small is rarely if ever defined) in bioequivalence between products may create unintended health consequences. In general, the argument appears to be that bioavailability differences of 5-10% are clinically important. This argument is purported to be particularly relevant in the elderly or the acutely ill patient, although I am personally unaware of any solid evidence to support this hypothesis.

The best method to compare two treatments is a randomized controlled trial that is designed to investigate clinically relevant endpoints. When it comes to warfarin, three randomized, crossover studies have been published to date. These studies involved 55, 57 and 113 patients, respectively. (3-5) In each of these three trials, the investigators were unable to find any statistically or clinically important differences in INR, dosage change requirements, or bleeding complications between the generic and brand name products. However, these trials were all single-blinded and some authors have suggested that dropouts in the first two trials may have compromised the validity of their findings. (6-7) There is also no doubt that these trials were underpowered to detect important differences in severe bleeding complications but they were likely of sufficient size to detect clinically important INR variations. In addition, these studies were all sponsored by the manufacturer of the generic product, and are thus susceptible to the same biases (or lack thereof, depending on your opinion) as studies sponsored by a brand name company.

Nevertheless, let us assume, for the sake of argument that these three trials were fatally flawed and thus uninterpretable. In 1998, over \$500 million US was spent on oral anticoagulants and 18% of this market went to the makers of generic warfarin. (3) That means the brand name manufacturers of warfarin lost close to \$100 million in sales in a single year. It seems unfathomable that a company that is losing that amount of business a year would not spend, say, \$2-3 million to conduct a well-designed trial designed to clearly address the issue of potential inequality if, in fact, that company truly believed there were clinically important differences between these products. The apparent lack of such published studies is, in my mind, far more telling than the existence of the three published generic company sponsored trials!

While I was reviewing the literature on the topic of NTI drugs and the differences between generic and brand name products, a number of other issues and questions came to mind that continue to puzzle me. I thought other clinicians might find these questions thought provoking as well:

1. As mentioned above, if there really are important clinical differences between generic and brand name products, why have the brand name companies who stand to lose millions of dollars, not done studies to definitively prove a clinically important difference between generic and brand name drugs?
2. If tablet-to-tablet and lot-to-lot differences of +/- 5-10% are allowed by most regulatory agencies, why are these variations in labeled potency not hotly debated?
3. If variations in dosing of 5% are so important, why are oral dosage forms not available that allow for dosage adjustments of this same magnitude?
4. If the FDA is correct and their studies have shown that the mean AUC differences between generic and brand name warfarin average only 3.5% (3), why is there concern?
5. If a reduction in potency of 5% is acceptable for shelf-life determination, why is this variation in potency not considered an important health problem?
6. If day-to-day physiological changes and changes in the timing of doses can produce fluctuations in levels of at least 20-30% for many drugs, why haven't we recognized this as a factor that is creating important health problems?
7. If peak-to-trough drug concentration variations during a dosing interval can be at least 30-50%, why is this not a reason for concern?
8. If the current bioequivalence standards are unacceptable, what should they be and what

evidence is there that this will improve the safety profile of the drugs we use?

9. Since pharmacodynamic and disease state variability is likely far greater than pharmacokinetic differences, it may be fruitless to worry about product-to-product bioavailability variations of less than 10%.
10. If the tools we use to measure blood concentrations often have an inherent variability of at least 5%, does this not somewhat overshadow the issue?
11. If missed doses and different meal times can produce variations of 20-30% in serum concentrations, should this be promoted as a major health issue?
12. If most so called "therapeutic ranges" are at least 2-fold, why would 5-10% differences in AUC be important?
13. Some clinicians suggest that the elderly or the acutely ill patients are at risk, but why would they absorb medications manufactured by different companies any more variably than other patients?
14. If the formulations of the products used in initial testing are often not the same as the marketed product, why is it acceptable not to do bioavailability tests on these reformulations?
15. When companies change their manufacturing process, why are they only required to submit bioavailability data?
16. Is there any legitimate physiological or pharmacodynamic reason why two products that are bioequivalent would produce a different therapeutic effect?
17. Why do brand name companies suggest that different looking generics could create a health problem because of confusion yet often put in legal blocks to prevent companies from using the same "packaging"?

My point in bringing up all these questions is to entice readers to put this issue into a proper context. I think we all wish that pharmaceutical companies (both brand name and generic) would sponsor more well-designed clinical comparative trials (not just to address generic-brand equivalence) in an attempt to definitively address important product comparison questions. Instead they seem to spend an inordinate amount of time and money debating these types of issues in both the advertising and the legal arena.

I think it is about time that we got on with doing research in more important areas than the generic versus brand name issue. We've all got more important patient care issues to address.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;6:200-203.

Stent versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction: What is the Therapy of Choice to STOP An MI?

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Original Citation

Schomig A, Kastrati A, Dirschinger J, Mehilli J, Schricke U, Pache J, Martinoff S, Neumann FJ, Schwaiger M. Coronary stenting plus platelet glycoprotein IIb/IIIa blockade compared with tissue plasminogen activator in acute myocardial infarction. Stent versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction Study Investigators. N Engl J Med. 2000;343:385-91. [PubMed Citation](#)

Overall Study Question

This "Stent versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction" (STOPAMI) Study was conducted to determine whether or not stenting combined with blockage of glycoprotein IIb/IIIa receptors (abciximab) leads to a greater degree of myocardial salvage and better clinical outcomes at 6 months in patients with acute myocardial infarction than thrombolysis with a "front-loaded, accelerated" tPA regimen. Patients presenting within 12 hours after the onset of chest for at least 20 minutes, and had ST-segment elevation of at least 0.1 mV in two or more limb leads or at least 2 mV in two or more contiguous leads on ECG were eligible for the study. The primary endpoint was the myocardial salvage (i.e. final minus initial defect) as determined by the salvage index (i.e. percentage of the left ventricle that was salvaged, divided by the percentage that was compromised by the initial perfusion defect). The secondary endpoint was a composite of death, myocardial infarction or stroke within 6 months of randomization.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. All patients received aspirin 500 mg, unfractionated heparin (UFH) 5000 U bolus. Immediately after randomization, patients received an intravenous injection of 27mCi (1000 MBq) of technetium Tc 99m sestamibi for single-photon-emission computed tomography that was performed in 6-8 hours after injection of the radionuclide. This was accomplished prior to initiation of the assigned therapy. Patients assigned to the accelerated, front-loaded tPA regimen received a 3-part dosing protocol consisting of an initial 15 mg bolus, followed by 0.75 mg/kg (maximum 50 mg) dose over 30 minutes, and finally a 0.5 mg/kg (maximum 35 mg) dose over 60 minutes. This was given in combination with UFH 1000 U/h to maintain the activated partial thromboplastin time (aPTT) between 60-85s for 48 hours. Those patients assigned to the stent arm received an additional dose of UFH 2500 U intraarterially, along with abciximab 0.25 mg/kg IV bolus prior to stent placement followed by 10 mcg/min for 12 hours following the intervention.

During the intervention, patients also received an additional 2500 U dose of UFH intraarterially. Post-interventional therapy included ticlopidine 250 mg orally twice daily x 4 weeks. All patients received aspirin 100 mg orally twice daily indefinitely.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Of the 140 patients who were enrolled, 71 were randomized to stenting plus abciximab group while 69 were randomized to the tPA group. Only one patient in the stent group did not receive the assigned therapy as the culprit artery opened during the injection of contrast medium and no angiographically significant stenosis requiring a stent was visible. The initial radionuclide study could not be performed in six patients in the stent group and 7 patients in the tPA group because of hemodynamic instability or for technical reasons. Of the 127 patients who underwent an initial radionuclide study, two from each group did not undergo follow-up study. Thus 123 patients (63 in the stent group and 60 in the tPA group) were evaluable for the primary endpoint.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

For the primary outcome of myocardial salvage index, all measurements were performed in the scintigraphic core laboratory by operators who were unaware of the patients' assigned therapy. The mean (+/- SD) intraobserver and interobserver variations in the measurement of the size of the defect were 2 +/- 3% and 2 +/- 3% of the left ventricle, respectively. However, patients and clinicians were not blinded to the treatment allocation.

4. Were the groups similar at the start of the trial?

Yes. The baseline characteristics of both groups were similar with regards to age, gender,

medications prior to admission, Killip class and vital signs. Past medical history was also similar with respect to hypertension, diabetes but slightly more patients in the tPA and compared to the stent group had a previous myocardial infarction at 14.9% and 9.9%, respectively and coronary artery bypass grafting (CABG) at 4.3% and 1.4%, respectively. The median time from admission to balloon inflation in the stent group was significantly longer (65 minutes, 25 and 75 percentiles of 53 and 85 minutes, respectively) compared to admissions to initiation of study drug in the tPA group (30 minutes, 25 and 75 percentiles of 23 and 40 minutes, respectively).

5. Aside from the experimental intervention, were the groups treated equally?

There were no reported differences in the further treatment of patients assigned to the stent group or tPA group.

What were the Results?

1. How large was the treatment effect?

The size of the perfusion defect was similar in the two groups, the final size of the infarct was significantly smaller among patients in the stent group than among those in the tPA group (14.3% versus 19.4% of the left ventricle ($p=0.02$)). This was the result of greater myocardial salvage in the stent group (16.1% versus 7.4%) of the left ventricle ($p<0.001$). Therefore the salvage index, the primary endpoint, was significantly greater in stenting than with tPA (0.57 versus 0.26, $p<0.001$).

The secondary endpoint of survival the composite endpoint of death, myocardial infarction or stroke at 6 months was reached in 8.5% of the stent group as compared with 23.2% with the tPA group (relative risk [RR] 0.34 95% confidence interval [CI] 0.13-0.88). The cumulative incidence of death during this period was 4.2% in the stent group and 13% in the tPA group (RR 0.31, 95% CI 0.08-1.16). Revascularization of the infarct-related vessel was needed in 10% of patients in the stent group and 34.4% of the patients in the tPA group (RR 0.24, 95% CI 0.11-0.57).

Adverse effects were not reported in this trial.

2. How precise was the estimate of the treatment effect?

The 95% CI for the primary endpoint were not provided. The 95% CI for the secondary endpoint of the composite endpoint did not include zero, indicating statistical significance.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. The use of abciximab in conjunction with stenting following acute myocardial infarction appears to be superior in preserving myocardial tissue as well as may potentially extrapolate to a reduction in further morbidity and mortality compared to medical management with tPA.

2. Were all clinically important outcomes considered?

No. Although this trial was able to demonstrate a benefit in the surrogate endpoint of myocardial salvage and in the composite clinical endpoint of death, myocardial infarction and stroke, no report of adverse of effect was provided. The salvage index is considered to be a valid surrogate marker that has been correlated to clinical outcomes in some small trials and a valid and accepted means of assessing myocardial damage. It would have useful to have adverse effect rates for this trial especially bleeding rates and clinically relevant thrombocytopenia.

3. Are the likely treatment benefits worth the potential harms and costs?

Unable to determine. this published trial leaves many unanswered questions with regard to the safety and economic impact of an invasive compared to non-invasive treatment strategy for acute myocardial infarction. As mentioned above, no adverse effect rates were reported in this trial and this prevents us from drawing any conclusions regarding the safety of the interventions. In addition, no economic evaluation was performed comparing the various treatment strategies.

Commentary

The STOPAMI Study demonstrates that primary stenting combined with abciximab therapy results in significantly greater myocardial salvage and better clinical outcomes than does thrombolysis with tPA in patients with acute myocardial infarction. Unfortunately, it fails to provide adequate safety comparison between these two treatment strategies. Nevertheless, this trial addresses a few important issues with respect to the overall management of acute myocardial infarction.

First, this trial provides supporting evidence to the already significant body of literature that primary angioplasty is at least as effective and in some patients superior to thrombolysis following AMI. The most recent American Heart Association (AHA) Guidelines endorsees primary angioplasty and an appropriate alternative to thrombolysis in these patients provided the institution performs greater than 200 angioplasty procedure per year and door-to-balloon time is no longer than 90 minutes. (1) Although the door-to-balloon time in this trial was significantly longer than door-to-needle time in the tPA group, it was well within the acceptable time frame outlined in the AHA Guidelines.

Second, this trial supports the growing body of literature that abciximab provides improved outcomes when used as adjuvant to angioplasty with or without stenting. Data from the EPIC demonstrate that abciximab as adjunctive therapy to angioplasty reduced the composite triple endpoint of death, MI or need for urgent revascularization (PTCA or CABG) at 3 years compared to placebo at 41.1% and 47.2% ($p=0.009$), respectively in high-risk patients which included those with evolving MI within 12 hours of

chest pain. (2) The EPILOG trial confirmed these results in patients undergoing both elective and emergent angioplasty with reduction in the same primary composite endpoint compared to placebo at 6 months (22.3% and 25.8% ($p=0.04$)). (3) Finally, results from the EPISTENT trial demonstrated the abciximab was also beneficial compared to placebo in reducing the incidence of the composite triple endpoint of death, MI or need for urgent revascularization (PTCA or CABG) at 30 days at 3.0% and 7.8% ($p<0.001$), respectively in patients requiring stent implantation. (4)

Finally, this trial raises the contentious issue of which glycoprotein IIb/IIIa receptor antagonists should be used in patients with AMI undergoing direct angioplasty. Clearly as mentioned above, all of the evidence published to date in this high-risk patient population supports the use of abciximab. However, despite alternative GP IIb/IIIa receptor antagonists such as eptifibatide and tirofiban demonstrating benefit in high-risk acute coronary syndrome patients with unstable angina (UA) and non-ST-segment elevation MI (NSTEMI trial) in patients, trials specifically evaluating the use of eptifibatide and tirofiban as an adjuvant to angioplasty procedures have failed to demonstrate benefit compared to placebo in this high risk subset of AMI patients. (5-8) The majority of evidence for adjunctive GP IIb/IIIa receptor antagonists with primary angioplasty is with abciximab and the STOPAMI trial reinforces that significantly greater myocardial salvage and better clinical outcomes can be achieved compared to thrombolysis with tPA in patients with AMI. This trial is also one of the first to compare direct angioplasty with adjuvant GP IIB/IIIa receptor antagonist to thrombolysis in patients with AMI and although the primary endpoint was myocardial survival and the trial was underpowered to conclude anything definitive with regards to clinical endpoints, the results would suggest that the benefits achieved in the early abciximab trials may be realized in patients with AMI undergoing direct angioplasty.

The jury is still out on alternative GP IIb/IIIa agents in this setting and patient population and the use of eptifibatide or tirofiban have not demonstrated the same favorable outcomes as abciximab has in high-risk patients. Consequently, the use of these newer agents should be discouraged until further studies are conducted to fully clarify their role in this setting.

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The Journal of Informed Pharmacotherapy

Stent versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction: What is the Therapy of Choice to STOP An MI?

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Original Citation

Schomig A, Kastrati A, Dirschinger J, Mehilli J, Schricke U, Pache J, Martinoff S, Neumann FJ, Schwaiger M. Coronary stenting plus platelet glycoprotein IIb/IIIa blockade compared with tissue plasminogen activator in acute myocardial infarction. Stent versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction Study Investigators. *N Engl J Med.* 2000;343:385-91.

Overall Study Question

This "Stent versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction" (STOPAMI) Study was conducted to determine whether or not stenting combined with blockage of glycoprotein IIb/IIIa receptors (abciximab) leads to a greater degree of myocardial salvage and better clinical outcomes at 6 months in patients with acute myocardial infarction than thrombolysis with a "front-loaded, accelerated" tPA regimen. Patients presenting within 12 hours after the onset of chest for at least 20 minutes, and had ST-segment elevation of at least 0.1 mV in two or more limb leads or at least 2 mV in two or more contiguous leads on ECG were eligible for the study. The primary endpoint was the myocardial salvage (i.e. final minus initial defect) as determined by the salvage index (i.e. percentage of the left ventricle that was salvaged, divided by the percentage that was compromised by the initial perfusion defect). The secondary endpoint was a composite of death, myocardial infarction or stroke within 6 months of randomization.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. All patients received aspirin 500 mg, unfractionated heparin (UFH) 5000 U bolus. Immediately after randomization, patients received an intravenous injection of 27mCi (1000 MBq) of technetium Tc 99m sestamibi for single-photon-emission computed tomography that was performed in 6-8 hours after injection of the radionuclide. This was accomplished prior to initiation of the assigned therapy. Patients assigned to the accelerated, front-loaded tPA regimen received a 3-part dosing protocol consisting of an initial 15 mg bolus, followed by 0.75 mg/kg (maximum 50 mg) dose over 30 minutes, and finally a 0.5 mg/kg (maximum 35 mg) dose over 60 minutes. This was given in combination with UFH 1000 U/h to maintain the activated partial thromboplastin time (aPTT) between 60-85s for 48 hours. Those patients assigned to the stent arm received an additional dose of UFH 2500 U intraarterially, along with abciximab 0.25 mg/kg IV bolus prior to stent placement followed by 10 mcg/min for 12 hours following the intervention.

During the intervention, patients also received an additional 2500 U dose of UFH intraarterially. Post-interventional therapy included ticlopidine 250 mg orally twice daily x 4 weeks. All patients received aspirin 100 mg orally twice daily indefinitely.

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2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Of the 140 patients who were enrolled, 71 were randomized to stenting plus abciximab group while 69 were randomized to the tPA group. Only one patient in the stent group did not receive the assigned therapy as the culprit artery opened during the injection of contrast medium and no angiographically significant stenosis requiring a stent was visible. The initial radionuclide study could not be performed in six patients in the stent group and 7 patients in the tPA group because of hemodynamic instability or for technical reasons. Of the 127 patients who underwent an initial radionuclide study, two from each group did not undergo follow-up study. Thus 123 patients (63 in the stent group and 60 in the tPA group) were evaluable for the primary endpoint.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

For the primary outcome of myocardial salvage index, all measurements were performed in the scintigraphic core laboratory by operators who were unaware of the patients' assigned therapy. The mean ($\pm$ SD) intraobserver and interobserver variations in the measurement of the size of the defect were $2 \pm 3\%$ and $2 \pm 3\%$ of the left ventricle, respectively. However, patients and clinicians were not blinded to the treatment allocation.

4. Were the groups similar at the start of the trial?

Yes. The baseline characteristics of both groups were similar with regards to age, gender, medications prior to admission, Killip class and vital signs. Past medical history was also similar with respect to hypertension, diabetes but slightly more patients in the tPA and compared to the stent group had a previous myocardial infarction at 14.9% and 9.9%, respectively and coronary artery bypass grafting (CABG) at 4.3% and 1.4%,

respectively. The median time from admission to balloon inflation in the stent group was significantly longer (65 minutes, 25 and 75 percentiles of 53 and 85 minutes, respectively) compared to admissions to initiation of study drug in the tPA group (30 minutes, 25 and 75 percentiles of 23 and 40 minutes, respectively).

5. Aside from the experimental intervention, were the groups treated equally?

There were no reported differences in the further treatment of patients assigned to the stent group or tPA group.

What were the Results?

1. How large was the treatment effect?

The size of the perfusion defect was similar in the two groups, the final size of the infarct was significantly smaller among patients in the stent group than among those in the tPA group (14.3% versus 19.4% of the left ventricle ($p=0.02$)). This was the result of greater myocardial salvage in the stent group (16.1% versus 7.4%) of the left ventricle ($p<0.001$). Therefore the salvage index, the primary endpoint, was significantly greater in stenting than with tPA (0.57 versus 0.26, $p<0.001$).

The secondary endpoint of survival the composite endpoint of death, myocardial infarction or stroke at 6 months was reached in 8.5% of the stent group as compared with 23.2% with the tPA group (relative risk [RR] 0.34 95% confidence interval [CI] 0.13-0.88). The cumulative incidence of death during this period was 4.2% in the stent group and 13% in the tPA group (RR 0.31, 95% CI 0.08-1.16). Revascularization of the infarct-related vessel was needed in 10% of patients in the stent group and 34.4% of the patients in the tPA group (RR 0.24, 95% CI 0.11-0.57).

Adverse effects were not reported in this trial.

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Will the Results Help Me in Caring for My Patients? Commentary

1. Can the results be applied to my patient care?

Yes. The use of abciximab in conjunction with stenting following acute myocardial infarction appears to be superior in preserving myocardial tissue as well as may potentially extrapolate to a reduction in further morbidity and mortality compared to medical management with tPA.

2. Were all clinically important outcomes considered?

No. Although this trial was able to demonstrate a benefit in the surrogate endpoint of myocardial salvage and in the composite clinical endpoint of death, myocardial infarction and stroke, no report of adverse effect was provided. The salvage index is considered to be a valid surrogate marker that has been correlated to clinical outcomes in some small trials and a valid and accepted means of assessing myocardial damage. It would have useful to have adverse effect rates for this trial especially bleeding rates and clinically relevant thrombocytopenia.

3. Are the likely treatment benefits worth the potential harms and costs?

Unable to determine. this published trial leaves many unanswered questions with regard to the safety and economic impact of an invasive compared to non-invasive treatment strategy for acute myocardial infarction. As mentioned above, no adverse effect rates were reported in this trial and this prevents us from drawing any conclusions regarding the safety of the interventions. In addition, no economic evaluation was performed comparing the various treatment strategies.

The STOPAMI Study demonstrates that primary stenting combined with abciximab therapy results in significantly greater myocardial salvage and better clinical outcomes than does thrombolysis with tPA in patients with acute myocardial infarction. Unfortunately, it fails to provide adequate safety comparison between these two treatment strategies. Nevertheless, this trial addresses a few important issues with respect to the overall management of acute myocardial infarction.

First, this trial provides supporting evidence to the already significant body of literature that primary angioplasty is at least as effective and in some patients superior to thrombolysis following AMI. The most recent American Heart Association (AHA) Guidelines endorse primary angioplasty and an appropriate alternative to thrombolysis in these patients provided the institution performs greater than 200 angioplasty procedure per year and door-to-balloon time is no longer than 90 minutes. (1) Although the door-to-balloon time in this trial was significantly longer than door-to-needle time in the tPA group, it was well within the acceptable time frame outlined in the AHA Guidelines.

Second, this trial supports the growing body of literature that abciximab provides improved outcomes when used as adjuvant to angioplasty with or without stenting. Data from the EPIC demonstrate that abciximab as adjunctive therapy to angioplasty reduced the composite triple endpoint of death, MI or need for urgent revascularization (PTCA or CABG) at 3 years compared to placebo at 41.1% and 47.2% ($p=0.009$), respectively in high-risk patients which included those with evolving MI within 12 hours of chest pain. (2) The EPILOG trial confirmed these results in patients undergoing both elective and emergent angioplasty with reduction in the same primary composite endpoint compared to placebo at 6 months (22.3% and 25.8% ($p=0.04$)). (3) Finally, results from the EPISTENT trial demonstrated the abciximab was also beneficial compared to placebo in reducing the incidence of the composite triple endpoint of death, MI or need for urgent revascularization (PTCA or CABG) at 30 days at 3.0% and 7.8% ($p<0.001$), respectively in patients

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($p < 0.001$), respectively in patients requiring stent implantation. (4)

Finally, this trial raises the contentious issue of which glycoprotein IIb/IIIa receptor antagonists should be used in patients with AMI undergoing direct angioplasty. Clearly as mentioned above, all of the evidence published to date in this high-risk patient population supports the use of abciximab. However, despite alternative GP IIb/IIIa receptor antagonists such as eptifibatide and tirofiban demonstrating benefit in high-risk acute coronary syndrome patients with unstable angina (UA) and non-ST-segment elevation MI (NSTEMI trial) in patients, trials specifically evaluating the use of eptifibatide and tirofiban as an adjuvant to angioplasty procedures have failed to demonstrate benefit compared to placebo in this high risk subset of AMI patients. (5-8) The majority of evidence for adjunctive GP IIb/IIIa receptor antagonists with primary angioplasty is with abciximab and the STOPAMI trial reinforces that significantly greater myocardial salvage and better clinical outcomes can be achieved compared to thrombolysis with tPA in patients with AMI. This trial is also one of the first to compare direct angioplasty with adjuvant GP IIb/IIIa receptor antagonist to thrombolysis in patients with AMI and although the primary endpoint was myocardial survival and the trial was underpowered to conclude anything definitive with regards to clinical endpoints, the results would suggest that the benefits achieved in the early abciximab trials may be realized in patients with AMI undergoing direct angioplasty.

The jury is still out on alternative GP IIb/IIIa agents in this setting and patient population and the use of eptifibatide or tirofiban have not demonstrated the same favorable outcomes as abciximab has in high-risk patients. Consequently, the use of these newer agents should be discouraged until further studies are conducted to fully clarify their role in this setting.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;6:204-205.

Effectiveness of St John's Wort: Does this Complementary Medication Work for Major Depression?

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Reviewer's profession/specialty: Psychiatric Pharmacy/Psychopharmacology

Original Citation

Shelton RC, Keller MB, Gelenberg A, Dunner DL, Hirschfeld R, Thase ME, Russell J, Lydiard RB, Crits-Cristoph P, Gallop R, Todd L, Hellerstein D, Goodnick P, Keitner G, Stahl SM, Halbreich U. Effectiveness of St John's wort in major depression: a randomized controlled trial. JAMA 2001 Apr 18;285(15):1978-86.

[PubMed Citation](#)

Overall Study Question

The objective of this study was to compare the efficacy and safety of a standardized extract of St. John's wort with placebo in outpatients with major depression. The subjects included 200 adult outpatients (mean age 42.4 years; 67% female; 85.9% white) with a Hamilton Rating Scale for Depression (HAM-D) score of at least 20. The primary outcome measure was HAM-D. Secondary measures included Beck Depression Inventory (BDI), Hamilton Rating Scale for Anxiety (HAM-A), Global Assessment of Function (GAF), and the Clinical Global Impression-Severity and -Improvement (CGI-S and CGI-I).

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. The intervention included a one week, single-blind, placebo run-in period and then patients were randomly assigned to receive either St. John's wort extract (n=98; 900 mg/d for 4 weeks, increased to 1200 mg/d in the absence of an adequate response thereafter) or placebo (n=102) for 8 weeks.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. 75/98 St. John's wort subjects completed the study compared to 86/102 placebo subjects completed the 8-week trial. All of those who do not complete the trial were accounted for.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes.

4. Were the groups similar at the start of the trial?

Yes. The only difference was that the placebo group had a greater score on the HAM-A (i.e. the placebo group likely had a greater level of anxiety at baseline), although actual scores were not provided.

5. Aside from the experimental intervention, were the groups treated equally?

Yes.

What were the Results?

1. How large was the treatment effect?

The rate of change in HAM-D scores showed a significant time effect, but not a significant treatment effect (i.e. there was no difference between interventions). Complete remission was greater for the St. John's wort group ($p=0.02$), however, this finding should be interpreted with caution since the rate for both groups was extremely low (14/98-St. John's wort; 5/102-placebo). In those patients that completed the trial, there was no significant difference in response rates. Furthermore, there was no significant difference between groups when the subjects were analyzed based on their initial severity of depression.

2. How precise was the estimate of the treatment effect?

The eight week response rate was 26.5% for St. John's wort (95% CI 18.7%-36.2%) and 18.6% for placebo (95% CI 12.1%-27.5%). When looking at remission rate, for St. John's wort, it was 14.3% (95% CI 8.6%-22.8%) versus 4.9% for placebo (95% CI 2.0%-11.3%)

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

This study validates the fact that St. John's wort has yet to be proven efficacious in a population with DSM-IV Major Depression.

2. Were all clinically important outcomes considered?

Yes. All major treatment effects and outcome factors associated with depression trials were considered and assessed in this trial.

3. Are the likely treatment benefits worth the potential harms and costs?

No. Considering the fact that suicide is a potential outcome in a patient with major depression, especially if untreated, the use of St. John's wort is not recommended at this time. Regarding side effects, the only major side effect of St. John's wort was headache, which occurred in 41% of the subjects versus 25% in placebo patients ($p=0.02$).

Commentary

Thus far, there have been many meta-analyses that have investigated the efficacy of St. John's wort. Due to methodological flaws, it has been difficult to draw conclusions from these previous studies. Schrader recently published a well designed study in which St. John's wort was found to be as effective as fluoxetine for the treatment of mild depression. However, this current was conducted in a more severely ill population. Based upon their findings, St. John's wort should not be recommended as a treatment option for major depressive episodes at this time.

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Reviewer's email address: levin@cop.ufl.edu

Reviewer's profession/specialty: Psychiatric Pharmacy/Psychopharmacology

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;6:206-208.

Power of the Placebo: Mighty or Meager?

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Reviewer's profession/specialty: Pharmacoepidemiology/Outcomes research/Rheumatology(Funded by CIHR fellowship)

Original Citation

Hrobjartsson A, Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. N Engl J Med 2001;344:1594-602. [PubMed Citation](#)

Overall Study Question

Since Beecher authored a paper in 1955 entitled "The Powerful Placebo", it has long been assumed that a placebo can exert a therapeutic effect in as high as 35% of cases. However, the problem with many of these evaluations is that they have estimated the effect of placebo as the difference from baseline in the condition of patients in the placebo group of a randomized trial after treatment. Thus, the effects of the placebo treatment could simply be statistical or disease-related artifacts (e.g. regression to the mean, natural course of the disease, etc.) that are independent of any effect of the placebo itself.

The authors of this quantitative systematic review set out to determine what the clinical effects of placebo as a treatment for disease was rather than determining its effect when used as a comparison treatment in clinical trials. To accomplish this, the authors selected randomized trials comparing a placebo group to an untreated group (for any disease state). The secondary objective of this review was to determine if the effect of placebo differed for subjective versus objective treatment outcomes.

Are the Results of the Study Valid?

1. Did the overview address a focused clinical question?

The clinical question was focused in the sense that there was an answerable research

question (i.e. does placebo exert an effect beyond that seen with no treatment?); however, due to the differences in placebos and the vast number of diseases and outcomes being studied, the question was somewhat broad to have direct applicability to any particular clinical situation.

2. Were the criteria used to select articles for inclusion appropriate?

The complete search strategy has been published on the New England Journal of Medicine website (www.nejm.org). In addition, the authors utilized appropriate a priori criteria to select studies for the review.

3. Is it unlikely that important, relevant studies were missed?

Since the authors used Medline, EMBASE, PsycLIT, Biological abstracts and the Cochrane Controlled trials registry, manually reviewed the reference lists at the end of each article and reviewed the literature of five languages (although which ones were not specifically identified), it unlikely that any important articles were missed.

4. Was the validity of the included studies appraised?

Although the authors did not appear to make use of a formal, validated scoring technique, they each independently reviewed the articles and extracted data using standardized forms. Disagreements were resolved through discussion between the authors.

5. Were assessments of studies reproducible?

Considering the above standardized technique for data extraction, the assessments of the studies were likely reproducible.

6. Were the results similar from study to study?

Since the diseases being studied were often different, and since the placebo being utilized could be defined as pharmacological (e.g. a lactose tablet), physical (e.g. a machine turned off) or psychological (e.g. a nondirectional neutral discussion between a patient and treatment provider), the results of the individual studies tended to differ. Some of the differences were also likely due to sample size (i.e. smaller studies tended to show more positive effects for placebo).

What are the Results?

1. What are the overall results of the review?

Of 727 potentially eligible published trials, 114 were actually included in the review. Of these, the outcomes were considered binary in 32 trials, and continuous in 82 trials.

Since only trials with similar outcome measures (i.e., binary or continuous) were combinable, the authors reported the results in this fashion.

For binary outcome trials, the overall pooled relative risk of an unwanted outcome with placebo was 0.95 (95% CI 0.88-1.02). For trials with subjective outcomes, the pooled relative risk was 0.95 (95% CI 0.86-1.05) and, for those with objective outcomes, the pooled relative risk was 0.91 (95% CI 0.80 to 1.04).

For continuous data trials, the overall pooled standardized mean difference was -0.28 (95% CI -0.38 to -0.19). Thus, there appeared to be a beneficial effect of placebo on continuous outcomes. When stratified further, this finding persisted for subjective trials only (pooled standardized mean difference of -0.36 (95% CI -0.47 to -0.25). For objective outcome trials, this beneficial effect was not noted (pooled standardized mean difference of -0.12 (95% CI -0.27 to 0.03).

As a secondary analysis, the authors analyzed data by disease where at least three trials were present that had similar outcomes. In the binary outcome trials, there were no benefits of placebo on the occurrence of nausea, depression or the ability to stop smoking. However, in the continuous outcome trials, there was only a significant reduction in pain intensity. Differences between treatment groups for other variables such as weight loss, mean diastolic blood pressure, and time to fall asleep were not significant.

2. How precise were the results?

As seen from the data above, the 95% CI were relative tight around the estimate.

3. How much does allowance for uncertainty change the results?

There was significant heterogeneity among the trials with binary outcomes. In a sensitivity analysis, it was shown that this heterogeneity was not due to small trials that often have a more pronounced effect of placebo. There was also significant heterogeneity among the trials of continuous outcomes and this was found to be, at least partially, due to the effect of the placebo diminishing with an increased sample size.

Will the results help me in caring for my patients?

1. Can the results be applied to my patient care?

Yes. These results can aid the clinician in the interpretation of research that involves a placebo group. In addition, although placebo treatment has been advocated in clinical practice due to its perceived benefit, this overview adds to the evidence that, regardless of ethical concern, adding a placebo to a patients therapeutic plan is unlikely to be successful.

2. Were all clinically important outcomes considered?

Due to the vast number of disease states and outcomes being studied, it is difficult to say if all clinically important outcomes were considered. However, the authors point out that they were unable to identify any trials that included quality of life as an outcome. Thus, the results of this review cannot be extended to include this outcome.

3. Are the benefits worth the harms and costs?

Due to the heterogeneity in both the disease states, types of placebos and endpoints, this issue is difficult to assess. However, due to the null results for the pooled endpoints, it is unlikely that the use of placebo is worth both the potential harm (i.e. patient deception, delayed therapy) and costs (i.e. sham equipment requirements, provider resources).

Commentary

Although some clinicians have advocated the clinical use of placebo therapy, this study adds credence to the arguments that placebos should not be used outside the boundaries of randomized controlled trials. (1) However, due to the heterogeneity that existed when combining trials using both objective and subjective outcomes due to the large numbers of diseases and outcomes being investigated, it is difficult to make any recommendations on a disease basis. In addition, as the authors point out, many of these studies were of weak design and often involved small sample sizes. The fact that smaller studies showed higher benefits of placebo than larger studies, adds to the methodologic limitations of this review due to the heterogeneous nature of the studies being evaluated. It is possible that placebo may have an effect of pain intensity, but this should be the focus of new research in the area as should studies examining quality of life outcomes. Therefore, the role for placebos as a therapy remains unproven, although there still is room for further investigation using appropriate studies.

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Power of the Placebo: Mighty or meager?

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Since the diseases being studied were often different, and since the placebo being utilized could be defined as pharmacological (e.g. a lactose tablet), physical (e.g. a machine turned off) or psychological (e.g. a nondirectional neutral discussion between a patient and treatment provider), the results of the individual studies tended to differ. Some of the differences were also likely due to sample size (i.e. smaller studies tended to show more positive effects for placebo).

What were the Results?

1. What are the overall results of the review?

Of 727 potentially eligible published trials, 114 were actually included in the review. Of these, the outcomes were considered binary in 32 trials, and continuous in 82 trials. Since only trials with similar outcome measures (i.e., binary or continuous) were combinable, the authors reported the results in this fashion.

For binary outcome trials, the overall pooled relative risk of an unwanted outcome with placebo was 0.95 (95% CI 0.88-1.02). For trials with subjective outcomes, the pooled relative risk was 0.95 (95% CI 0.86-1.05) and, for those with objective outcomes, the pooled relative risk was 0.91 (95% CI 0.80 to 1.04).

For continuous data trials, the overall pooled standardized mean difference was -0.28 (95% CI -0.38 to -0.19). Thus, there appeared to be a beneficial effect of placebo on continuous outcomes. When stratified further, this finding persisted for subjective trials only (pooled standardized mean difference of -0.36 (95% CI -0.47 to -0.25). For objective outcome trials, this beneficial effect was not noted (pooled standardized mean difference of -0.12 (95% CI -0.27 to 0.03).

As a secondary analysis, the authors analyzed data by disease where at least three trials were present that had similar outcomes. In the binary outcome trials, there were no benefits of placebo on the occurrence of nausea, depression or the ability to stop smoking. However, in the continuous outcome trials, there was only a significant reduction in pain intensity. Differences between treatment groups for other variables such as weight loss, mean diastolic blood pressure, and time to fall asleep were not significant.

2. How precise were the results?

As seen from the data above, the 95% CI were relative tight around the estimate.

3. How much does allowance for uncertainty change the results?

There was significant heterogeneity among the trials with binary outcomes. In a sensitivity analysis, it was shown that this heterogeneity was not due to small trials that often have a more pronounced effect of placebo. There was also significant heterogeneity among the trials of continuous outcomes and this was found to be, at least partially, due to the effect of the placebo diminishing with an increased sample size.

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Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. These results can aid the clinician in the interpretation of research that involves a placebo group. In addition, although placebo treatment has been advocated in clinical practice due to its perceived benefit, this overview adds to the evidence that, regardless of ethical concern, adding a placebo to a patient's therapeutic plan is unlikely to be successful.

2. Were all clinically important outcomes considered?

Due to the vast number of disease states and outcomes being studied, it is difficult to say if all clinically important outcomes were considered. However, the authors point out that they were unable to identify any trials that included quality of life as an outcome. Thus, the results of this review cannot be extended to include this outcome.

3. Are the likely treatment benefits worth the potential harms and costs?

Due to the heterogeneity in both the disease states, types of placebos and endpoints, this issue is difficult to assess. However, due to the null results for the pooled endpoints, it is unlikely that the use of placebo is worth both the potential harm (i.e. patient deception, delayed therapy) and costs (i.e. sham equipment requirements, provider resources).

Commentary

Although some clinicians have advocated the clinical use of placebo therapy, this study adds credence to the arguments that placebos should not be used outside the boundaries of randomized controlled trials. (1) However, due to the heterogeneity that existed

when combining trials using both objective and subjective outcomes due to the large numbers of diseases and outcomes being investigated, it is difficult to make any recommendations on a disease basis. In addition, as the authors point out, many of these studies were of weak design and often involved small sample sizes. The fact that smaller studies showed higher benefits of placebo than larger studies, adds to the methodologic limitations of this review due to the heterogeneous nature of the studies being evaluated. It is possible that placebo may have an effect of pain intensity, but this should be the focus of new research in the area as should studies examining quality of life outcomes. Therefore, the role for placebos as a therapy remains unproven, although there still is room for further investigation using appropriate studies.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;6:209-212.

Glucosamine Sulphate: Add it to the List of Effective Alternatives for Osteoarthritis?

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Reviewer's profession/specialty: Doctor of Pharmacy Student, University of British Columbia

Original Citation

Reginster JY, Derolsy R, Rovati LC, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. Lancet 2001;375:251-6. [PubMed Citation](#)

Overall Study Question

This trial was conducted over a 3-year period to determine if glucosamine sulphate can affect the progression of symptoms and joint structure changes for osteoarthritis involving the knee.

Three hundred and fifteen patients from an outpatient Bone and Cartilage Research Unit in Belgium were screened and 212 patients over 50 years of age (mean age 66 years) with primary knee osteoarthritis in the medial femorotibial compartment (mean duration of osteoarthritis 7.8 years) were included in the study. Patients were previously diagnosed as per clinical and radiological criteria of the American College of Rheumatology. Severity of disease was based on the Kellgren and Lawrence radiographic system. Exclusion criteria included history or active presence of other rheumatic diseases potentially responsible for a secondary osteoarthritis, severe articular inflammation as confirmed by physical exam and laboratory parameters (ESR <40 mm/h and serum rheumatoid factor titre <1:40), traumatic knee lesions, overweight individuals (BMI>30 kg/m²), abnormal hematologic, hepatic, renal or metabolic functions and intra-articular or systemic use of corticosteroids in the 3 months preceding enrolment.

Patients were allocated to receive glucosamine sulphate 1500 mg (powder for oral solution) or placebo once daily for 3 years.

The main outcome measures were joint structural changes (changes in joint space width measured by

weight bearing, anteroposterior radiographs of each knee at baseline, 1 and 3 years) and symptoms of osteoarthritis (as per Western Ontario and McMaster Universities (WOMAC) osteoarthritis index). Secondary outcome measures included use of rescue medications, withdrawal rates, occurrence of adverse events and routine safety laboratory test.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Randomization was computer-generated in blocks of 4, and participants were randomized in chronological order.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. Two hundred and twelve patients were randomized and 139 completed the trial (71 placebo, 68 glucosamine). Seventy-three patients withdrew from the trial (35 placebo, 38 glucosamine). Eighteen placebo and 21 glucosamine recipients withdrew due to adverse events, 12 vs. 14 were lost to follow-up and 5 vs. 3 withdrew due to a lack of effect in the placebo and glucosamine groups, respectively. The data was analyzed based on intention-to-treat principles.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. Patients, investigators and radiology technicians were blind to the treatment allocation. The principal investigator was provided with individual envelopes containing patient codes.

4. Were the groups similar at the start of the trial?

Yes. Baseline characteristics were similar among the treatment groups. Summation of visual analogue scale scores of the WOMAC index were slightly higher for the glucosamine sulphate group as compared to placebo (1030.2 mm vs. 939.7 mm). The mean joint space width (mm) was similar between the groups (5.39 placebo vs. 5.23 glucosamine sulphate) however, there was a baseline measure missing from the glucosamine group. The absence of this data could affect conclusions made from assessing changes in joint space narrowing from baseline values.

5. Aside from the experimental intervention, were the groups treated equally?

Yes.

What were the Results?

1. How large was the treatment effect?

The authors evaluated the data by way of 3 analytical methods including intention-to-treat (last observation carried forward), intention-to-treat (worst case scenario) and FINALLY, analysis of those patients who completed 3 years of the trial. Data of the latter methods are reported below.

Mean joint space narrowing (mm) in the medial compartment of the tibiofemoral joint with intention to treat analysis (worst case scenario) was -0.31 (-0.48 to -0.13) in the placebo group (n=106) vs. -0.06 (-0.22 to 0.09) in the glucosamine sulphate group (n=106) yielding a difference of 0.24 (0.01 to 0.48) (p=0.043). Minimum joint space narrowing (mm) was -0.40 (-0.56 to -0.24) in the placebo group versus -0.07 (-0.22 to 0.07), difference of 0.33 (0.12 to 0.54) (p=0.003).

Mean joint space narrowing (mm) in the medial compartment of the tibiofemoral joint including patients completing 3 years was -0.31 (95% CI -0.57 to -0.04) in the placebo group (n=71) versus 0.07 (-0.17 to 0.32) in the glucosamine sulphate group (n=68) yielding a difference of 0.38 (0.02 to 0.73) (p=0.038). Minimum joint space narrowing (mm) was -0.40 (-0.64 to -0.17) in the placebo group versus 0.11 (-0.10 to 0.33), difference of 0.51 (0.20 to 0.83) (p=0.002).

At 3 years, 32/106 placebo patients and 16/106 patients in the glucosamine sulphate group had severe joint space narrowing (defined as narrowing of the joint by more than 0.5 mm). The RR was 0.5 (0.3 to 0.9) with an ARR of 15 (4% to 26%), NNT to benefit one patient over 3 years was 7 (4 to 26).

Average percent change in total WOMAC scores after three years based on intention to treat worst case scenario were 9.8% (-6.2 - 25.8%) for the placebo group and -11.6% (-20.3 to -3.2%) in the glucosamine group with a difference between groups of 21.6% (95% CI 3.5 to 39.6%) (p=0.020). Average percent change in total WOMAC scores after three years based on patients assessed for 3 years were 9.8% (-14.6 to 34.3%) for the placebo group and -24.3% (-37.0 to -11.6%) in the glucosamine group with a difference between groups of 34.1% (6.4 to 61.8%) (p=0.016).

Patients in both groups were reported to have taken rescue analgesics on average of one out of six days throughout the study duration. Differences between the groups in analgesia rescue were reported to be non-significant but this data is not presented in the text. The incidence of side effects were similar between the groups with 93% and 94% of patients experiencing at least one side effect in the placebo group and glucosamine group, respectively.

The correlation between between structure and symptom changes was poor. Correlation between the variables was assessed using Spearman's correlation test, however the data was not provided in the text.

2. How precise was the estimate of the treatment effect?

The difference in mean joint space narrowing between the groups was statistically significant favoring the treatment group versus the placebo for intention to treat analysis ($p=0.043$). Confidence intervals surrounding the point estimates for the placebo and glucosamine sulphate groups for mean joint space narrowing (mm) were overlapping and wide thereby indicating clinical significance of the results is less clear.

The NNT for joint space narrowing was 7 (95% CI 4 - 26). The significance of this finding as it pertains to clinical outcomes can be difficult to interpret as the correlation between this outcome and clinical symptoms was not significant in this trial.

The difference in the WOMAC index scores between the groups was statistically significant, but the confidence intervals were overlapping and wide. The desired percent change in WOMAC index score was not stated a priori in the text.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. The results can be applied to patients with primary knee osteoarthritis with mild to moderate severity of symptoms.

2. Were all clinically important outcomes considered?

Yes. Clinically important indicators pertinent to osteoarthritis are included in the WOMAC index. Such measures include pain, stiffness and limitation of physical function. Joint space narrowing was the surrogate marker (main outcome of interest) but the correlation of this endpoint was not correlated to clinical symptoms in this trial. Quality of life was not evaluated in the trial.

3. Are the likely treatment benefits worth the potential harms and costs?

Yes. In patients with mild to moderate primary knee osteoarthritis, glucosamine serves as an alternative with the potential to reduce joint space narrowing and improve symptoms associated with knee osteoarthritis. This trial provides long-term data with respect to safety of this agent and can provide a reasonable therapeutic alternative for patients unable to tolerate side effects of conventional therapy.

Commentary

This study provides long-term data for the use of glucosamine sulphate in patients with osteoarthritis. The body of literature continues to grow with positive results for the use of this agent. (1) Previous trials performed with this agent were of shorter duration and although efficacy data was obtained,

safety data was lacking.

There are numerous methodologic issues of the trial study that may influence the interpretation of the results. The potential for variability in outcome measures of radiographic measurements, the variability of commercially available glucosamine products, and lack of correlation between joint space narrowing and clinical symptoms are important factors to consider when evaluating the results of this trial. Other methodologic issues that need to be considered include a lack of description for the placebo, the use of rescue analgesia and minimal follow-up and data collection throughout the trial. The generalizability of the results of this trial in populations with osteoarthritis in joints other than the knee CANNOT BE advocated.

The decision-making process for clinicians seeking effective treatments for osteoarthritis involves analysis of the efficacy, toxicity and cost data for available pharmacotherapeutic alternatives. Goals of therapy primarily include symptomatic relief and results of this study indicate that a trial of 1500 mg of glucosamine sulphate daily in patients with mild to moderate osteoarthritis (as per symptoms and radiographic findings) could provide such relief. The implications of decreased joint space narrowing attributed to use with glucosamine sulphate requires further long-term evaluation.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;6:213-217.

Lamivudine-Zidovudine for Prevention of Maternal-Infant Transmission of HIV-1: Is Combination Therapy Superior to Monotherapy?

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Original Citation

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Overall Study Question

To assess the safety of perinatal lamivudine-zidovudine therapy, especially in children, and its effects on viral load, acquisition of drug resistance, and maternal-infant transmission of HIV-1 in a nonbreastfeeding population. The patient population included HIV seropositive pregnant women registered in the French Perinatal Study observational database. The control group consisted of 899 pregnant women with HIV-1 who had received zidovudine monotherapy as the standard of care for the prevention of maternal-infant transmission from May 1994 to February 1997. The study cohort consisted of 445 HIV-1 positive pregnant women who received lamivudine in addition to the zidovudine prophylaxis regimen for the prevention of maternal-infant transmission. The outcome variables for this study included HIV-1 infection status and tolerance of therapy in children through 18 months of age, and maternal plasma HIV-1 RNA levels through 6 weeks after delivery were the primary outcome variable measured. The control group received zidovudine monotherapy according to the Pediatric AIDS Clinical Trial Group (ACTG) 076 (1) study as follows: Antepartum: Oral zidovudine 100mg five times daily, initiated at 14-34 weeks' gestation and continued throughout the pregnancy. Intrapartum: During labor, intravenous administration of zidovudine in a one-hour initial dose of 2mg/kg body weight,

followed by a continuous infusion of 1mg/kg body weight/hour until delivery. Postpartum: Oral administration of zidovudine to the newborn (zidovudine syrup 2mg/kg body weight/dose q6h or zidovudine intravenously 1.5 mg/kg body weight/dose q6h) for the first six weeks of life, beginning at eight-12 hours after birth. The cohort group received zidovudine which was administered using ACTG 076 based recommendations. (1) In addition, women received lamivudine 150mg bid begun at 32 weeks gestation and continued until delivery. Infants then received lamivudine 2mg/kg body weight per day for 6 weeks.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

No. The study was an open-label, nonrandomized intervention study which utilized an ongoing observational database for cohort and historical control patients.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

No. See description of study design above.

4. Were the groups similar at the start of the trial?

No. There were several differences between the cohort and control groups at baseline including: 1) significantly more patients with a history of intravenous drug use (IVDU) in the control group ($p = 0.04$); 2) significantly more patients born in sub-Saharan Africa in the cohort group ($p=0.02$); 3) significantly more patients who had an elective cesarean delivery in the cohort group ($p=0.005$); and 4) significantly more patients who were antiretroviral experienced in the cohort group ($p=0.001$).

Neither IVDU nor geographic origin are associated with a difference in maternal-fetal transmission of HIV. However, it is known that active IVDU significantly impairs patient adherence to antiretroviral therapy and that adherence to antiretroviral therapy is critical to maintaining virologic response. Therefore, it is possible that IVDU may be a confounding variable in the results of this study. Elective cesarean delivery is known to be protective, significantly decreasing the risk of maternal-fetal HIV transmission when used in combination with zidovudine monotherapy from about 6% to less than 2%.^(2,3) Thus, it is possible that imbalance in the number of patients having elective cesarean was a confounding factor which also favored the cohort group. Finally, the cohort group had significantly more patients who were antiretroviral experienced. This factor may be of

relevance in both response to therapy and in the incidence of resistance in both the mother and infant.

5. Aside from the experimental intervention, were the groups treated equally?

Unable to determine, although it appears that follow-up of patients in the historical control group and cohort were similar. This study was an observational one, using a historical control group, thus, it is difficult to determine whether care of patients was similar in both groups.

What were the Results?

1. How large was the treatment effect?

A sample size of 460 mother-infant pairs was calculated to allow for a difference in transmission rate from 6% in the historical control group to 3% in the treatment cohort, with a power of 80% and an alpha of 0.05. 95% confidence intervals were determined. Seven of 437 (1.6%) children in the treatment cohort were diagnosed as having HIV infection (95% CI 0.7%-3.3%). Data was available for 858 children born to women in the control group. The maternal-infant transmission rate (6.8%; 158/858; 95% CI, 5.1%-8.7%) in the control group was significantly higher than the treatment cohort ($p < 0.001$). When multivariate analysis was completed, adjusting for the mode of delivery, history of antiretroviral therapy, and maternal HIV disease progression, the frequency of maternal-infant HIV-1 transmission in the study group was 5-fold lower than in the control group.

The median decrease in viral load in paired samples of women was 1.24 log₁₀ copies/mL (range -1.63 to 3.4 log₁₀ copies/mL). Sixteen children (4%) had major birth defects. The incidence of major birth defects in children not exposed to antiretroviral drugs is in the range of 2-5%, therefore, the investigators concluded that the prevalence of major birth defects in the study group was not different than population values. Three children in the study group had mitochondrial toxicity, two of whom had a fatal neurological disorder and one child had a persistent increase in lipase. This corresponds to a prevalence of mitochondrial toxicity of 0.7% (3/452) (as calculated by this reviewer, not reported in the paper). The investigators indicate that the prevalence of mitochondrial cytopathies in the general population is estimated to be about 60 in 100,000 (0.06%).⁽⁴⁾ Therefore, the incidence of mitochondrial toxicity in children receiving lamivudine-zidovudine in this study appeared to be 10-fold higher than the general population (as calculated by this reviewer, not reported in the paper). The proportion of infants requiring blood transfusion, the frequency of moderate-to-severe anemia at birth or at 1 month of age, the frequency of moderate-to-severe neutropenia at birth or at 1 month of age did not differ between the treatment cohort and the historical control group.

The selection of virus with the lamivudine-resistant M184V mutation occurred in approximately one-third of women in the cohort, which may compromise the future efficacy of lamivudine. The M184V mutation occurred more frequently in women with high plasma HIV-1 RNA levels, low CD4 cell count, or both. These women would be

offered highly active antiretroviral therapy to maintain their own health, according to the most recent guidelines for management of HIV patients.⁽⁵⁾ The proportion of lamivudine-resistant virus increased with the duration of treatment, therefore if lamivudine-zidovudine therapy is selected, it may be prudent to begin therapy with lamivudine late in pregnancy and stop it promptly at delivery. There is concern that drug resistant HIV-1 mutant strains are not only of concern for the future care of the mother, but there is also a concern of transmission of drug resistant virus to the infant. In this study, 2 children were infected with lamivudine-resistant variants. However, the clinical significance of the lamivudine M184V mutation currently remains controversial, since: 1) the M184V mutation can reverse or prevent emergence of 215 reverse transcriptase mutation which is associated with resistance to zidovudine and other nucleoside analogs; 2) M184V mutation increases the activity of tenofovir (an investigational nucleotide reverse transcriptase inhibitor); and 3) M184V mutation decreases the replicative capacity or fitness of HIV virus.⁽⁶⁾

2. How precise was the estimate of the treatment effect?

The 95% confidence intervals for the prevalence of maternal-infant transmission of HIV-1 in both the cohort and control groups were relatively narrow and did not cross zero. The calculated absolute risk reduction (ARR) for maternal-infant transmission of HIV-1 between the cohort and control group was determined to be 5.2% $((7/437 - 58/858) \times 100 = 5.2\%)$ (as calculated by this reviewer, not reported in the paper). This corresponds to a number needed to treat (NNT) of 19 patients $(1/ARR = 1/0.052 = 19)$ (as calculated by this reviewer, not reported in the paper). The reduction in maternal-infant HIV-1 transmission looks quite impressive in this study. However, if the incidence of transmission in the cohort (1.6%) is compared to historical data using a combination of zidovudine and elective cesarean section (2%), then the ARR is only 0.4% and the NNT is 250. Therefore, combination antiretroviral therapy with lamivudine-zidovudine may not be clinically superior to a combination of zidovudine monotherapy with elective cesarean.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

The investigators of this study responsibly acknowledge that the implications for their findings for the prevention of maternal-infant HIV transmission are not clear. Although the addition of lamivudine to zidovudine may reduce the risk of infection in the infant, the relationship between incremental benefit and risk is undetermined, and needs to be compared to other preventive strategies used in healthy pregnant HIV positive women (e.g. zidovudine with elective cesarean). However, at this point in time, it may be appropriate for a physician to discuss both options (lamivudine-zidovudine with vaginal delivery or zidovudine monotherapy with elective cesarean) with their patients. Pregnant women with high viral load and/or low CD4 count will receive more aggressive combination therapy to maintain their own health, and the issues in these patients are different from those where antiretroviral drugs are used solely to prevent vertical transmission.^(5,7)

2. Were all clinically important outcomes considered?

Yes.

3. Are the likely treatment benefits worth the potential harms and costs?

See above.

Commentary

The question of monotherapy versus combination therapy to prevent maternal-fetal transmission of HIV is a clinically important one to address in practice today. Since the advent of highly active antiretroviral therapy, the use of combination antiretroviral therapy has been recommended. From around 1996, the dogma among HIV practitioners treating asymptomatic HIV positive patients has been to "hit hard, hit early". In the treatment of HIV positive pregnant women, consideration must be given to both the antiretroviral treatment of the woman's HIV infection and the antiretroviral prophylaxis to reduce perinatal HIV transmission. (8) Although data was lacking about safety and efficacy in pregnancy, combination therapy has been recommended in the treatment of pregnant women to manage their own HIV infection. However, in 2001, we are now observing that long-term use of these effective agents is associated with significant toxicities. As a result, the most recent guidelines (7) have recommended a "hit hard, but hit later" philosophy for the management of asymptomatic HIV positive patients.

The current recommendations for asymptomatic HIV positive patients is to offer treatment to patients: 1) with a CD4 count of greater than 200/mm³ but less than 350/mm³, regardless of viral load; and 2) with a CD4 count of greater than 350/mm³ and a viral load of >30,000 (bDNA) or >55,000 (RT-PCR).(7) Again, it is recommended that antiretroviral therapy in pregnancy reflect the practice in the general adult population.(5,7) Therefore, it is now feasible that healthy pregnant women with low viral load and high CD4 count may have antiretroviral therapy deferred during their pregnancy, for management of their HIV infection. However, we know that antiretroviral therapy and elective cesarean significantly reduce maternal-infant HIV transmission. Therefore, specific therapy to prevent vertical transmission will still be necessary in pregnant women.

Clinicians have assumed that combination therapy would be superior to monotherapy in preventing vertical transmission, and have been using combination therapy in the absence of data. Thus, the study question posed by these investigators was a very clinically relevant one for today's practice. That is, "Is combination therapy better than monotherapy to prevent vertical transmission of HIV-1?" Where this study fell short, however, was in the selection of the comparator group. In today's practice, a more clinically relevant comparator group would have been asymptomatic HIV positive pregnant women managed with zidovudine monotherapy along with elective cesarean. Although the study suggests that combination therapy with lamivudine-zidovudine was significantly better than monotherapy with zidovudine (1.6% vs. 6.8%, respectively), one cannot make direct conclusions from this study about combination therapy versus zidovudine monotherapy plus elective cesarean. Other studies have shown that the risk of vertical transmission when zidovudine monotherapy is combined with elective cesarean is less than 2%.(2,3) If the results of this study are compared to the historical data for zidovudine monotherapy plus cesarean, the results of combination therapy do not appear clinically superior (NNT

250 pregnant HIV positive women).

It is known that maternal morbidity and mortality in HIV negative women is greater after cesarean, as compared to vaginal delivery.(9,10) The data evaluating relative risk of cesarean among HIV positive versus HIV negative women is conflicting. (5) However, cesarean section is protective in reducing vertical transmission of HIV.(2,3)

A direct comparative study would be required to confirm this reviewer's conclusion that lamivudine-zidovudine does not appear clinically superior to zidovudine monotherapy plus cesarean. An evaluation of the risk of toxicity along with resistance issues for the women and infants with combination antiretroviral therapy needs to be weighed against the risks of cesarean in HIV positive women. The relationship between incremental benefit and risk of lamivudine-zidovudine therapy versus zidovudine monotherapy with elective cesarean is not known.

At this point in time, it may be appropriate for a physician to discuss both options (lamivudine-zidovudine with vaginal delivery or zidovudine monotherapy with elective cesarean) with their patients. The data from this study may be of assistance to consensus bodies, such as the Public Health Service Task Force, to use when developing recommendations regarding new perinatal regimens.(8)

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Lamivudine-Zidovudine for Prevention of Maternal-Infant Transmission of HIV-1: Is Combination Therapy Superior to Monotherapy?

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Original Citation

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Overall Study Question

To assess the safety of perinatal lamivudine-zidovudine therapy, especially in children, and its effects on viral load, acquisition of drug resistance, and maternal-infant transmission of HIV-1 in a nonbreast-feeding population. The patient population included HIV seropositive pregnant women registered in the French Perinatal Study observational database.

The control group consisted of 899 pregnant women with HIV-1 who had received zidovudine monotherapy as the standard of care for the prevention of maternal-infant transmission from May 1994 to February 1997. The study cohort consisted of 445 HIV-1 positive pregnant women who received lamivudine in addition to the zidovudine prophylaxis regimen for the prevention of maternal-infant transmission. The outcome variables for this study included HIV-1 infection status and tolerance of therapy in children through 18 months of

age, and maternal plasma HIV-1 RNA levels through 6 weeks after delivery were the primary outcome variable measured. The control group received zidovudine monotherapy according to the Pediatric AIDS Clinical Trial Group (ACTG) 076 (1) study as follows: Antepartum: Oral zidovudine 100mg five times daily, initiated at 14-34 weeks' gestation and continued throughout the pregnancy. Intrapartum: During labor, intravenous administration of zidovudine in a one-hour initial dose of 2mg/kg body weight, followed by a continuous infusion of 1mg/kg body weight/hour until delivery. Postpartum: Oral administration of zidovudine to the newborn (zidovudine syrup 2mg/kg body weight/dose q6h or zidovudine intravenously 1.5 mg/kg body weight/dose q6h) for the first six weeks of life, beginning at eight-12 hours after birth. The cohort group received zidovudine which was administered using ACTG 076 based recommendations. (1) In addition, women received lamivudine 150mg bid begun at 32 weeks gestation and continued until delivery. Infants then received lamivudine 2mg/kg body weight per day for 6 weeks.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

No. The study was an open-label, nonrandomized intervention study which utilized an ongoing observational database for cohort and historical control patients.

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2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

No. See description of study design above.

4. Were the groups similar at the start of the trial?

No. There were several differences between the cohort and control groups at baseline including: 1) significantly more patients with a history of intravenous drug use (IVDU) in the control group ($p = 0.04$); 2) significantly more patients born in sub-Saharan Africa in the cohort group ($p=0.02$); 3) significantly more patients who had an elective cesarean delivery in the cohort group ($p=0.005$); and 4) significantly more patients who were antiretroviral experienced in the cohort group ($p=0.001$).

Neither IVDU nor geographic origin are associated with a difference in maternal-fetal transmission of HIV. However, it is known that active IVDU significantly impairs patient adherence to antiretroviral therapy and that adherence to antiretroviral therapy is critical to maintaining virologic response. Therefore, it is possible that IVDU may be a confounding variable in the results of this study. Elective cesarean delivery is known to be protective, significantly decreasing the risk of maternal-fetal HIV transmission when used in combination with zidovudine monotherapy from about 6% to less than 2%.^(2,3) Thus, it is possible that imbalance in the number of patients having elective cesarean was a confounding factor which also favored the cohort group. Finally, the cohort group had significantly more patients who were antiretroviral experienced. This factor may be of relevance in both response to therapy and in the incidence of resistance in both the mother and infant.

5. Aside from the experimental intervention, were the groups treated equally?

Unable to determine, although it appears that follow-up of patients in the historical control group and cohort were similar. This study was an observational one, using a historical control group, thus, it is difficult to determine whether care of patients was similar in both groups.

What were the Results?

1. How large was the treatment effect?

A sample size of 460 mother-infant pairs was calculated to allow for a difference in transmission rate from 6% in the historical control group to 3% in the treatment cohort, with a power of 80% and an alpha of 0.05. 95% confidence intervals were determined. Seven of 437 (1.6%) children in the treatment cohort were diagnosed as having HIV infection (95% CI 0.7%-3.3%). Data was available for 858 children born to women in the control group. The maternal-infant transmission rate (6.8%; 158/858; 95% CI, 5.1%-8.7%) in the control group was significantly higher than the treatment cohort ($p<0.001$). When multivariate analysis was completed, adjusting for the mode of delivery, history of antiretroviral therapy, and maternal HIV disease progression, the frequency of maternal-infant HIV-1 transmission in the study group was 5-fold lower than in the control group.

The median decrease in viral load in paired samples of women was 1.24 log₁₀ copies/mL (range -1.63 to 3.4 log₁₀ copies/mL). Sixteen children (4%) had major birth defects. The incidence of major birth defects in children not exposed to antiretroviral drugs is in the range of 2-5%, therefore, the investigators concluded that the prevalence of major birth defects in the study group was not different than population values. Three children in the study group had mitochondrial toxicity, two of whom had a fatal neurological disorder and one child had a persistent increase in lipase. This corresponds to a prevalence of mitochondrial toxicity of 0.7% (3/452) (as calculated by this reviewer, not re-

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ported in the paper). The investigators indicate that the prevalence of mitochondrial cytopathies in the general population is estimated to be about 60 in 100,000 (0.06%).(4) Therefore, the incidence of mitochondrial toxicity in children receiving lamivudine-zidovudine in this study appeared to be 10-fold higher than the general population (as calculated by this reviewer, not reported in the paper). The proportion of infants requiring blood transfusion, the frequency of moderate-to-severe anemia at birth or at 1 month of age, the frequency of moderate-to-severe neutropenia at birth or at 1 month of age did not differ between the treatment cohort and the historical control group.

The selection of virus with the lamivudine-resistant M184V mutation occurred in approximately one-third of women in the cohort, which may compromise the future efficacy of lamivudine. The M184V mutation occurred more frequently in women with high plasma HIV-1 RNA levels, low CD4 cell count, or both. These women would be offered highly active antiretroviral therapy to maintain their own health, according to the most recent guidelines for management of HIV patients.(5) The proportion of lamivudine-resistant virus increased with the duration of treatment, therefore if lamivudine-zidovudine therapy is selected, it may be prudent to begin therapy with lamivudine late in pregnancy and stop it promptly at delivery. There is concern that drug resistant HIV-1 mutant strains are not only of concern for the future care of the mother, but there is also a concern of transmission of drug resistant virus to the infant. In this study, 2 children were infected with lamivudine-resistant variants. However, the clinical significance of the lamivudine M184V mutation currently remains controversial, since: 1) the M184V mutation can reverse or prevent emergence of 215 reverse transcriptase mutation which is associated with resistance to zidovudine and other nucleoside analogs; 2) M184V mutation increases the activity of tenofovir (an investigational nucleotide reverse transcriptase inhibitor); and 3) M184V mutation decreases the replicative capacity or fitness of HIV virus.(6)

2. How precise was the estimate of the treatment effect?

The 95% confidence intervals for the prevalence of maternal-infant transmission of HIV-1 in both the cohort and control groups were relatively narrow and did not cross zero. The calculated absolute risk reduction (ARR) for maternal-infant transmission of HIV-1 between the cohort and control group was determined to be 5.2% $((7/437 - 58/858) \times 100 = 5.2\%)$ (as calculated by this reviewer, not reported in the paper). This corresponds to a number needed to treat (NNT) of 19 patients $(1/ARR = 1/0.052 = 19)$ (as calculated by this reviewer, not reported in the paper). The reduction in maternal-infant HIV-1 transmission looks quite impressive in this study. However, if the incidence of transmission in the cohort (1.6%) is compared to historical data using a combination of zidovudine and elective cesarean section (2%), then the ARR is only 0.4% and the NNT is 250. Therefore, combination antiretroviral therapy with lamivudine-zidovudine may not be clinically superior to a combination of zidovudine monotherapy with elective cesarean.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

The investigators of this study responsibly acknowledge that the implications for their findings for the prevention of maternal-infant HIV transmission are not clear. Although the addition of lamivudine to zidovudine may reduce the risk of infection in the infant, the relationship between incremental benefit and risk is undetermined, and needs to be compared to other preventive strategies used in healthy pregnant HIV positive women (e.g. zidovudine with elective cesarean). However, at this point in time, it may be appropriate for a physician to discuss both options (lamivudine-zidovudine with vaginal delivery or zidovudine monotherapy with elective cesarean) with

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their patients. Pregnant women with high viral load and or low CD4 count will receive more aggressive combination therapy to maintain their own health, and the issues in these patients are different from those where antiretroviral drugs are used solely to prevent vertical transmission. (5,7)

2. Were all clinically important outcomes considered?

Yes.

3. Are the likely treatment benefits worth the potential harms and costs?

See above.

Commentary

The question of monotherapy versus combination therapy to prevent maternal-fetal transmission of HIV is a clinically important one to address in practice today. Since the advent of highly active antiretroviral therapy, the use of combination antiretroviral therapy has been recommended. From around 1996, the dogma among HIV practitioners treating asymptomatic HIV positive patients has been to "hit hard, hit early". In the treatment of HIV positive pregnant women, consideration must be given to both the antiretroviral treatment of the woman's HIV infection and the antiretroviral prophylaxis to reduce perinatal HIV transmission. (8) Although data was lacking about safety and efficacy in pregnancy, combination therapy has been recommended in the treatment of pregnant women to manage their own HIV infection. However, in 2001, we are now observing that long-term use of these effective agents is associated with significant toxicities. As a result, the most recent guidelines (7) have recommended a "hit hard, but hit later" philosophy for the management of asymptomatic HIV positive patients.

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Clinicians have assumed that combination therapy would be superior to monotherapy in preventing vertical transmission, and have been using combination therapy in the absence of data. Thus, the study question posed by these investigators was a very clinically relevant one for today's practice. That is, "Is combination therapy better than monotherapy to prevent vertical transmission of HIV-1?" Where this study fell short, however, was in the selection of the comparator group. In today's practice, a more clinically relevant comparator group would have been asymptomatic HIV positive pregnant women managed with zidovudine monotherapy along with elective cesarean. Although the study suggests that combination therapy with lamivudine-zidovudine was significantly better than monotherapy with zidovudine (1.6% vs. 6.8%, respectively), one cannot make direct conclusions from this study about combination therapy versus zidovudine monotherapy plus elective cesarean. Other studies have shown that the risk of vertical transmission when zidovudine monotherapy is combined with elective cesarean is less than 2%.(2,3) If the results of this study are compared to the historical data for zidovudine monotherapy plus cesarean, the results of combination therapy do not appear clinically superior (NNT 250 pregnant HIV positive women).

It is known that maternal morbidity and mortality in HIV negative women is greater after cesarean, as compared to vaginal delivery.(9,10) The data evaluating relative risk of cesarean among HIV positive versus HIV negative women is conflicting. (5) However, ce-

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sarean section is protective in reducing vertical transmission of HIV.(2,3)

A direct comparative study would be required to confirm this reviewer's conclusion that lamivudine-zidovudine does not appear clinically superior to zidovudine monotherapy plus cesarean. An evaluation of the risk of toxicity along with resistance issues for the women and infants with combination antiretroviral therapy needs to be weighed against the risks of cesarean in HIV positive women. The relationship between incremental benefit and risk of lamivudine-zidovudine therapy versus zidovudine monotherapy with elective cesarean is not known.

At this point in time, it may be appropriate for a physician to discuss both options (lamivudine-zidovudine with vaginal delivery or zidovudine monotherapy with elective cesarean) with their patients. The data from this study may be of assistance to consensus bodies, such as the Public Health Service Task Force, to use when developing recommendations regarding new perinatal regimens. (8)

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Issues in Pharmacotherapy Practice

The Role of Anticoagulant and Antiplatelet Therapy in Percutaneous Coronary Intervention

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Abstract

Background: Unfractionated heparin (UFH) has traditionally been the anticoagulant of choice for prevention of thrombus formation during percutaneous coronary intervention (PCI). However, in the past several years, newer anticoagulants such as the intravenous platelet glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors were found to be important adjunctive therapy in PCI for reduction of death and non-fatal myocardial infarction. In addition, patients receiving an intracoronary stent have been shown to benefit from oral anti-platelet therapy with aspirin plus a thienopyridine for 2-4 weeks after the procedure.

Methods: A MEDLINE search (July 1966 - May 2001) was conducted to identify all publications evaluating the use of anticoagulant or antiplatelet agents during PCI. When available, randomized clinical trials were included. Some case-controlled and retrospective evaluations are included due to lack of randomized clinical trial data of certain agents.

Results: The appropriate intensity of anticoagulation with UFH is controversial. Low-molecular weight heparins or direct thrombin inhibitors may offer a better alternative to UFH in PCI in the future. Introduction of potent platelet inhibitors have increased the success of PCI, but at the expense of an increased bleeding complications. The impact of multiple anticoagulant and antiplatelet regimens on bleeding complications is unknown, especially in older, more debilitated populations.

Conclusions: Adjuvant antiplatelet and antithrombotic therapy are essential to improve ischemic outcomes after PCI. The challenge in the next few years will be to develop agents and dosing schemes that better balance the benefit of decreased ischemic complications with bleeding adverse effects.

J Inform Pharmacother 2001;6:300-313.

Introduction

Non-surgical revascularization of coronary arteries narrowed by atherosclerosis was first performed in 1977 (1). In recent years, percutaneous transluminal coronary angioplasty (PTCA) has been supplemented with other non-surgical revascularization techniques including directional atherectomy, rotational atherectomy

and coronary stenting. The term percutaneous coronary intervention (PCI) has been introduced to encompass all of these procedures.

Although PCI is generally safe, complications can occur including myocardial infarction (2.8%) and death (2%) (2). Dilatation of a stenotic coronary artery causes plaque rupture and exposure of the sub-endothelium (3). These events are powerful stimuli for activation of the coagulation cascade and aggregation of platelets. Fatal and non-fatal myocardial infarction (MI) are typically caused by platelet aggregation and thrombus formation at the site of vessel injury, platelet microemboli formation that occludes smaller vessels downstream, or both (3).

Unfractionated heparin (UFH) has traditionally been the anticoagulant of choice for prevention of thrombus formation during PCI (1). However, in the past several years, newer anticoagulants such as the intravenous platelet glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors were found to be important adjunctive therapy in PCI for reduction of death and non-fatal MI (4-10).

Recent data indicates that as many as 70% of all patients undergoing a percutaneous intervention will receive a coronary stent (2). Stenting has clearly been effective in decreasing the need for repeat interventions, but the risk of precipitating thrombosis and distal thrombus embolization downstream from the stent are thought to be problematic (2). Acute administration of potent anti-platelet agents are thought to prevent early thrombotic occlusion of the stent, and concomitant oral anti-platelet therapy with aspirin and a thienopyridine for 2-4 weeks after the procedure has been shown to decrease the incidence of delayed or sub-acute stent thrombosis (occurring 2 to 30 days after the procedure) (11).

Although this multi-pronged approach appears to be effective in decreasing the thrombus formation and the subsequent risk of MI, this benefit needs to be balanced against the real risk of increased bleeding events. The challenge in the next several years will be in determining how to safely use these agents in combination, and in developing agents that provide protection against thrombosis and MI without increasing the risk for adverse bleeding events. The purpose of this review is to outline the history of anticoagulation and antiplatelet therapy in PCI, to discuss the evidence for the efficacy and safety of these agents in this setting, and to discuss new pharmacologic developments that hold promise in this area.

The Role of Unfractionated Heparin in Percutaneous Coronary Interventions

Data from a variety of preclinical and clinical trials indicate that anti-thrombin treatment is a necessary adjunct for PCI (12-15). The clinical need for anti-thrombin treatment is reinforced by data from diagnostic cardiac catheterization showing 50% reductions in death and MI among 125,000 patients treated with UFH compared to 125,000 with no UFH (16). Thrombin plays a crucial role in the cascade of reactions leading to thrombus formation at the site of endothelial injury. In addition, thrombin is involved in post-thrombotic events such as attraction of inflammatory cells and the regulation of growth of endothelial and vascular smooth muscle cells (17). Nevertheless, ideal dosing and monitoring of UFH during PCI remains controversial.

Unfractionated Heparin Monitoring

Although the activated partial thromboplastin time (aPTT) is traditionally used to measure the intensity of UFH anticoagulation, the need for a point of care measurement device makes the activated clotting time

(ACT) the preferred monitoring parameter for UFH therapy during PCI. In addition, ACT values are linearly related to UFH levels, whereas aPTT levels become unmeasurable when high UFH concentrations are achieved as is the case during PCI (18). Two commercially available point-of-care monitoring devices for ACT are widely used; the HemoTec (HemoTec Inc, Englewood, CO) and Hemochron (International Technidyne Corporation, Edison, NJ) devices. The Hemochron device gives values 30-50 seconds (s) higher than the HemoTec at all UFH concentrations (19).

Early recommendations for ACT-guided monitoring of UFH dose during PCI came from the cardiopulmonary bypass literature and were based on observations that thrombosis occurred on membrane oxygenators found in cardiopulmonary bypass circuits at ACT values less than 300 s (20). In non-human primate experiments, fibrin monomer can be detected in the bypass circuit at ACT values below 400 s (21). Consequently, an ACT value between 300 s and 400 s has been proposed as a threshold for anticoagulation during PCI. Current guidelines promoted by the American College of Chest Physicians (ACCP) recommend using a target ACT value of 250 s to 300 s with the HemoTec device and 300 s to 350 s with the Hemochron device (11). However, most studies investigating the effects of peri-procedural UFH intensity on angiographic and clinical outcomes have been retrospective and nonrandomized. As a result, the efficacy of anticoagulation when the ACT is maintained at these values remains controversial.

Case Control Studies

A case-control study evaluated 186 subjects from a series of 1290 patients undergoing non-emergent angioplasty (13). Hemochron ACTs in 62 patients who experienced ischemic complications after angioplasty (cases) were compared to 124 matched patients without complications (controls). All patients received aspirin and 10,000 U of UFH as a bolus prior to PCI. Adverse clinical outcomes were defined as death, MI, or need for urgent revascularization. Relative to the control population, patients who experienced adverse clinical outcomes had significantly lower initial and minimum ACTs. The odds ratio for adverse outcomes among patients with ACT $\geq$ 300 s compared with ACT $<$ 300 s was 0.34 (95% confidence interval [CI], 0.15 to 0.77).

Ferguson et al. reviewed 1469 consecutive PTCA procedures performed at a single center using a case-control analysis (14). Activated clotting times of 103 patients with major in-hospital complications (cases) were compared to 400 randomly selected, matched, uncomplicated patients from the same series (controls). All patients had ACTs measured at baseline, after UFH therapy, and at the end of the procedure. There were no differences in baseline ACTs between the two groups. Adverse clinical outcomes included death and urgent or emergent bypass surgery. Patients with subsequent complications had significantly lower ACTs after UFH therapy and at the end of the procedure. There were 63/103 cases with initial HemoTec ACT $<$ 250 seconds, and 108/400 control patients with ACT $<$ 250 seconds. The odds ratio for adverse outcomes was 0.23 (95% CI, 0.15 to 0.37).

McGarry et al. analyzed 487 consecutive patients who underwent elective angioplasty at single center (8). A total of 336 patients had documented aPTT. Patients were divided into two groups: those with aPTT $\geq$ 3 times the control value (n=271), and those with aPTT $<$ 3 times the control value (n=65). Blood samples were obtained after the procedure and before discontinuation of UFH for sheath removal. Clinical outcomes included death and ischemic complications (chest pain with $>$ 1 mm ST segment elevation in the dilated territory associated with elevation in creatine kinase MB fraction) prior to hospital discharge. There was a

statistically significant reduction in the incidence of ischemic events (1.5% vs. 9.2%, $p < 0.001$) in patients with aPTT values ≥ 3 times the control value at hospital discharge. There were 7 complications in the 65 patients with PTT < 3 times the control value, and 7 complications in the 271 patients with PTT ≥ 3 times the control value. The odds ratio for adverse outcomes was 0.22 (95% CI, 0.08 to 0.65).

Randomized Trials

Unfractionated heparin dosing for anticoagulation during elective PCI has been compared in two small, randomized trials. Vainer et al. randomized a total of 404 patients with stable angina undergoing PCI to receive either 5000 units (205 patients) or 20,000 units (199 patients) of UFH intravenously as a bolus prior to the procedure (22). The mean ACT was 209 ± 69 s for low dose and 381 ± 117 s for high dose patients measured by the HemoTec device. The composite endpoint of death, MI, repeat PCI or acute occlusion was observed in 27/204 patients (13.2%) receiving low dose UFH and in 16/199 patients (8.0%) receiving high dose UFH (odds ratio [OR] 1.74; 95% CI 0.91-3.35).

Boccarda et al. randomized 400 patients to high fixed dose UFH bolus (15,000 U) or a weight-adjusted UFH (100 U/kg) (23). Additional UFH bolus doses were administered if the procedure lasted more than one hour or at the discretion of the operator if complications appeared. Patients were monitored using aPTT. Clinical endpoints were defined as death, Q- or non-Q wave MI, unplanned repeat PTCA, CABG or bailout stenting, and major hemorrhage. The average total UFH dose actually received was $15,300 \pm 888$ U in the high fixed dose group and 8251 ± 2027 U in the weight-adjusted group, corresponding to doses of 208 ± 41 and 110 ± 22 U/kg body weight respectively. Stents were placed in 28.5% and 26.5% of patients respectively. The primary endpoint (freedom from death, myocardial infarction, unplanned revascularization or bailout stenting) occurred in 91% and 95% of patients in the high-fixed and low-weight adjusted dose groups respectively (OR 1.88; 95% CI 0.80-4.50, $p = 0.12$).

Post-procedural Unfractionated Heparin

Two studies have evaluated the utility of post-procedural intravenous UFH after uncomplicated PCI (24,25). Both found that serious bleeding complications were increased. Evaluation of serious bleeding complications between post-procedural subcutaneous UFH and intravenous UFH was compared in another trial. Bleeding rates were significantly lower in the group receiving subcutaneous UFH, but ischemic complications were similar between the two groups (26). Due to the potential to increase the risk of serious bleeding complications, routine post-procedural UFH infusions are not recommended for uncomplicated PCI.

Alternatives to Unfractionated Heparin in Percutaneous Coronary Interventions

Newer developments such as the use of low-molecular-weight derivatives of UFH and direct antagonists of thrombin may be useful in improving the safety and efficacy of anticoagulation during interventional procedures.

Low-Molecular-Weight Heparins

The low-molecular-weight heparins (LMWH) are produced by enzymatic or chemical degradation of UFH, and consist of smaller polysaccharide chains with higher ratios of anti-Xa:anti-IIa activity than UFH (27). Low-

molecular-weight heparins have become increasingly popular within the last several years, in large part as a consequence of their ease of use as well as two trials indicating possible superiority of enoxaparin compared with UFH in patients presenting with non-ST-segment elevation acute coronary syndromes (NSTEMI ACS) (28,29).

At present, experience with LMWH in PCI consists of three safety registries and a small, randomized trial. The one randomized trial, Reduction of Restenosis After PTCA, Early Administration of Reviparin in a Double-Blind, Unfractionated Heparin and Placebo-Controlled Evaluation (REDUCE) was performed in 1993 and 1994 (30). In this trial, the LMWH reviparin (7,000 U bolus followed by infusion and subcutaneous injection) was compared with UFH (10,500 U bolus followed by infusion) in 612 patients. Platelet glycoprotein IIb/IIIa receptor antagonists were not used and stents were implanted only for abrupt closure. The primary endpoint, a composite of ischemic events at six months was not different between the two groups; however in the reviparin-treated group, the rate of rescue stent implantation on the day of the PCI was reduced from 6.9% to 2%.

Three safety registries evaluated the use of enoxaparin in PCI have been developed. The National Investigators Collaborating on Enoxaparin (NICE) group recently published results of the NICE-1 and NICE-4 studies, and the NICE-3 data was discussed at the Transcatheter Therapeutics Conference in 2000 (31-33). In the NICE-1 registry, patients received enoxaparin 1.0 mg/kg as an intravenous bolus prior to PCI (30). In the NICE-4 registry, patients received 0.75 mg/kg of intravenous enoxaparin in addition to traditional doses of abciximab (31). Within these studies, levels of anti-Xa activity were similar to levels that have been reported in patients treated with a 10,000 U bolus of UFH (37,38). In the NICE-3 registry, the safety of enoxaparin 1 mg/kg subcutaneously in combination with all three GPIIb/IIIa inhibitors were evaluated in 616 patients with NSTEMI ACS (31). In this evaluation, 292 patients underwent PCI and received no UFH. If the PCI was performed <8 hours after the enoxaparin administration, no additional anticoagulation was used. If the PCI was performed >8 hours after enoxaparin administration, 0.3 mg/kg of enoxaparin was given intravenously (32). Observations from all registries appear promising in that the rates of bleeding were similar compared with historical controls (Table I). It should be noted that these trials were observational and designed to evaluate safety, not efficacy endpoints. These preliminary investigations should be a firm foundation for the design of large-scale randomized trials in the future that will be powered to detect efficacy differences.

Table I. Summary of Safety Findings from Low-Molecular-Weight Heparin Registries

Study	Treatment	Frequency of Clinically Significant Bleeds (%)	
		Major CABG	Major Non-CABG
NICE-1 (30)	Enoxaparin 1mg/kg	1.1	0.5
NICE -3 (32)	Enoxaparin 1mg/kg	6.7	4.4
	+tirofiban	5.1	1.4
	+eptifibatide	4.4	3.2
	+abciximab	4.1	0.7
NICE-4 (31)	Enoxaparin 0.75 mg/kg + abciximab	0.4	0.2

Direct Thrombin Inhibitors

The development of direct thrombin inhibitors has been based on the characterization of hirudin, a 65-amino acid polypeptide isolated from the salivary gland of the medicinal leech that is a potent irreversible inhibitor of thrombin. Hirudin binds to thrombin at the catalytic site and also at the anion binding exosite by an anionic hirudin tail fragment (33). Commercially available direct thrombin inhibitors include argatroban, lepirudin, and bivalirudin.

Argatroban is a synthetic direct thrombin inhibitor derived from L-arginine indicated for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT) (34). Unlike bivalirudin and lepirudin, argatroban is eliminated hepatically rather than renally. Pilot studies using it in PCI patients with and without HIT indicate that it may be safe and effective. Larger, randomized trials need to be performed to determine safety, efficacy and an optimal dosing regime.

Lepirudin is a recombinant hirudin derivative which binds specifically and irreversibly to thrombin. Approximately 50% of the drug is eliminated renally, so the dose should be adjusted in patients with significant renal impairment. Similar to argatroban, some case reports have been published using lepirudin in PCI in patients with HIT, but little other data are available (35).

Bivalirudin is a synthetic peptide derivative of hirudin with unique thrombin binding characteristics. Initially, bivalirudin binding is non-competitive and complete. However, thrombin recognizes bivalirudin as a substrate and cleaves the D-Phe-Phe-Arg-Pro moiety of bivalirudin, thereby freeing the active binding site of thrombin once again. This vacates thrombin's active site and leaves in place the bivalirudin moiety binding competitively to thrombin's fibrin binding site. In this configuration, thrombin is able to recognize other competing substrates and participate in the coagulation process to maintain hemostasis (36). Bivalirudin is currently the only direct thrombin inhibitor indicated for replacing UFH during PCI by the United States Food and Drug Administration.

In a multi-center trial, 4,312 patients with severe, accelerating or rest angina within the last month and suitable coronary-artery lesions were randomly treated with UFH (n=2151), or bivalirudin (n=2161) and PCI (37,38). The primary endpoint was defined as a combination of death, MI (enzymatically or clinically defined), or the need for repeat revascularization in the first 7-days, with specified follow-up at 90-days and 6-months. The combined clinical endpoint occurred in 7.9% of patients in the UFH group, and in 6.2% of patients in the bivalirudin group (OR 0.78; 95% CI 0.62-0.99 p=0.039). Absolute differences were maintained at 90-days (p=0.012), but were no longer statistically significant at 6-months (p=0.15). Among a pre-stratified and separately randomized group of 741 patients with post-MI unstable angina, the combined clinical endpoint occurred in 37 (9.9%) of 372 patients in the UFH group, and in 18 (4.9%) of 369 patients in the bivalirudin group (OR 0.47; 95% CI 0.26-0.84 p=0.009). Differences were maintained out to 30 days (p=0.003) and 6 months (p=0.049). Clinically significant bleeding complications occurred in 9.3% of patients in the UFH group and 3.5% of patients in the bivalirudin group (OR 0.34; 95% CI 0.26-0.45, p<0.001). The reduction in bleeding complications was driven by lower transfusion rates (p<0.001) and lower major bleeds associated with ≥ 5 g/dl decrease in hemoglobin concentration (p<0.001) among patients assigned bivalirudin (37). The main limitations of this trial are that it was performed in the early 1990's, prior to the introduction and widespread use of stents and GPIIb/IIIa inhibitors. In addition, the initial dose of UFH during PCI was much higher than currently utilized doses (175 u/kg), and post-procedural UFH was prescribed for 18-24 hours per protocol which could have lead to a higher incidence of bleeding complications in the UFH group. Ongoing trials are currently investigating the safety and efficacy of

bivalirudin in contemporary interventional cardiology practice (39,40).

The Role of Anti-platelet Agents in Percutaneous Coronary Interventions

Percutaneous coronary intervention is complicated by platelet activation which may lead to adverse events after these procedures. Administration of aspirin reduces complications of ischemia after PCI, although the minimum effective aspirin dosage is unknown (11). One study of low-dose (80 mg/day) compared with high dose (1500 mg/day) aspirin found no difference in MI or the need for coronary artery bypass surgery (41). Since higher doses can be associated with gastrointestinal irritations, lower empiric doses (80-325 mg daily) are recommended in PCI (11). When possible, it is probably prudent to administer aspirin at least 2 hours prior to the procedure (11). Although other agents also prevent early complications after angioplasty, none has been shown to be superior to aspirin (42, 43).

Thienopyridines

The thienopyridines, ticlopidine and clopidogrel, inhibit platelet aggregation induced by adenosine diphosphate (ADP) (44). Thienopyridines have been shown to improve outcomes when given in addition to aspirin in patients undergoing stent placement (45). Due to a perceived superior safety profile, clopidogrel has become the thienopyridine of choice for the prevention of stent thrombosis (46). Most of the data demonstrating a benefit of clopidogrel in patients with stents are in case-series or retrospective analysis using historical ticlopidine controls (Table II) (47-49). However, two randomized trials were recently published which confirm results from these smaller single-center studies (46,50).

Table II. Summary of Non-Randomized Observational Reports of the Safety and Efficacy of Clopidogrel in Patients Undergoing Stent Placement.

Study	Design	Regimen	Size (n)	Outcomes	Results
Berger (48)	Observational, consecutive stent placement	Clopidogrel 300 mg once then 75 mg/day for 2 weeks + abciximab	500	30 day combined endpoint of death, nonfatal MI, stent thrombosis and need for repeat revascularization or CABG	Death=0.4% MI=0.0% Revasc=0.4%
Moussa (47)	Retrospective, observational, successful stent placement on no GPIIb/IIIa	Ticlopidine 500mg once then 250 mg bid for 2 weeks or	1406	30 day death, MI, stent thrombosis, CABG, adverse drug reactions (ADRs)	Death=0.9% (T) vs. 1.0% (C) MI=1.8% (T) vs. 0.7% (C) Stent thrombosis=1.5% (T) vs. 1.4% (C) CABG=0.4% (T) vs. 0.7% (C) ADRs=10.6% (T) vs. 5.3% (C)
		Clopidogrel 300 mg once then 75 mg/d for 4 weeks	283		

Mishkel (49)	Consecutive stent placement	Clopidogrel 75 mg/d or Ticlopidine 250 mg bid at the operators discretion	514 361	30 day death, MI, stent thrombosis, urgent revascularization	Death=0.6% (T) vs. 0.9% (C) MI=0.6% (T) vs. 1.0% (C) Revasc=0.3% (T) vs. 0.6% (C)

One trial compared the safety of four weeks of ticlopidine 500 mg/day (n=345) to clopidogrel 75 mg/day (n=355) after successful stenting during elective or emergency PCI (50). All patients also received 100 mg of aspirin daily. They found no difference in the primary cardiac endpoint (cardiac death, urgent target vessel revascularization, angiographically determined thrombotic stent occlusions or non-fatal MI) within 30 days, but the trial was not powered to detect differences in efficacy. Cardiac events occurred in 11 patients taking clopidogrel (3.1%) and in 6 patients taking ticlopidine (1.7%). The primary noncardiac endpoint (death from noncardiac cause, severe hemorrhagic event, or adverse event causing discontinuation of study medication) occurred in 16 patients on clopidogrel (4.5%) compared with 33 patients assigned to ticlopidine (9.6%). Of note, this trial did not use the popular "loading dose" of clopidogrel which is commonly used in clinical practice.

In the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS) trial, 1020 patients were randomized after successful coronary stenting to a 28-day course of clopidogrel 75 mg daily with or without a 300 mg loading dose, or to 250 mg of ticlopidine twice daily (46). The primary endpoint of major peripheral bleeding complications, neutropenia, thrombocytopenia, or early discontinuation of study drug as the result of noncardiac adverse events was reached in 9.1% of patients on ticlopidine compared with 4.6% of patients on the combined clopidogrel regimens (RR 0.5; 95% CI 0.31 to 0.81; p=0.005). Overall rates of major adverse cardiac events were low and did not differ significantly between the three groups (0.9% with ticlopidine, 1.5% with 75 mg/d clopidogrel, 1.2% with clopidogrel loading, p=NS). Notably, the CLASSICS trial excluded patients undergoing PCI for primary angioplasty, patients whose baseline cardiac enzymes were greater than twice the upper limit of normal, those requiring a GPIIb/IIIa inhibitor, on oral anticoagulants and those who received a thrombolytic agent within 2 weeks prior to the procedure. In addition, patients requiring placement of more than two stents or stenting to more than one vessel were also excluded.

Neither of these trials were powered to detect differences in cardiac event rates, but ticlopidine consistently had lower event rates compared with clopidogrel. Nevertheless, because of its superior safety profile demonstrated in these two reports, clopidogrel is now considered the preferred thienopyridine in patients undergoing stent placement.

Phosphodiesterase Inhibitors

Cilostazol is an antiplatelet agent that increases the intracellular cyclic adenosine monophosphate concentrations by inhibiting phosphodiesterase III. Most research using cilostazol in PCI has focused on its effects on reducing the phenomena of restenosis (51). Restenosis is an abnormal type of vascular remodeling where smooth muscle cells proliferate in the intima of the artery resulting in reocclusion and the need for repeat interventions. In addition to its antiplatelet effects and inhibition of smooth muscle cell

proliferation, cilostazol is thought to enhance reendothelialization after PCI (51). Enhanced regeneration of the endothelium after stent placement would decrease the thrombogenicity of the stent, possibly decreasing cardiac events that may occur as a result of stent thrombosis. In one study, 409 patients were randomized to receive aspirin plus ticlopidine or aspirin plus cilostazol started two days prior to elective stent placement. Ticlopidine (250 mg twice daily) was given for one month post-stent placement, and cilostazol (200 mg twice daily) for six months post-stent placement. Follow-up angiography was performed at six months on 77% of patients. No cases of stent thrombosis were reported, and the restenosis rate was 27% in the ticlopidine group compared with 23% in the cilostazol group ($p=NS$) (52). However, diffuse type in-stent restenosis was significantly reduced by cilostazol (54% vs. 27%, $p<0.05$). In diabetic patients, restenosis was also significantly reduced by cilostazol (50% vs. 22%, $p<0.05$). Clinical events did not differ between the two groups.

Another study aimed to evaluate the efficacy of cilostazol for prevention of stent thrombosis. Four hundred and ninety patients were randomized to receive aspirin plus ticlopidine (250 mg twice daily) or aspirin plus cilostazol (200 mg twice daily) for one month. Major cardiac events were similar at 30 days in the two groups (2.9% vs. 1.6%, respectively). However this study was not powered to detect differences in clinical event rates. Withdrawal from therapy due to an adverse drug reaction occurred in 2.9% of patients on ticlopidine and 2.0% of patients on cilostazol ($p=NS$) (53).

Glycoprotein IIb/IIIa Inhibitors

Platelet aggregation is dependent on activation of the GPIIb/IIIa receptor, the final common pathway of platelet activation (54). The GPIIb/IIIa receptor is necessary for platelet binding to fibrinogen, which leads to subsequent formation of a platelet plug and eventually to an intracoronary thrombus if left unchecked. Inhibition of platelet activation using aspirin and UFH provides some benefit in PCI, but does not always insure optimal outcomes due to insufficient platelet inhibition. Specific inhibitors of the GPIIb/IIIa receptor used together with UFH, have been shown to improve outcomes of patients undergoing PCI compared with UFH alone (Table III) (4-10).

Table III. Summary of Placebo-controlled Glycoprotein IIb/IIIa Inhibitor Trials in Patients Undergoing Percutaneous Coronary Intervention.

Study	Agent	Patients (n)	Patient Population
EPIC (4)	Abciximab	2099	High risk PCI -MI within 12 hours -MI within 7 days -chest pain within 24 hours
EPILOG (5)	Abciximab	2792	Urgent or elective PCI -excluding unstable angina or MI within 24 hours
CAPTURE (6)	Abciximab	1265	Refractory unstable angina undergoing PCI -chest pain within 48 hours despite therapy with nitrates and intravenous UFH
RAPPORT (65)	Abciximab	483	STEMI within 12 hours
EPISTENT (7)	Abciximab	2399	Elective or urgent PCI with or without stent placement

ADMIRAL (66)	Abciximab	300	STEMI within 12 hours
CADILLAC (67)	Abciximab	2082	STEMI within 12 hours -excluding high risk anatomy, Killip Class IV
IMPACT II (8)	Eptifibatide	4010	All PCI
ESPRIT (10)	Eptifibatide	2064	Elective (non-urgent) PCI with stent placement -excluding saphenous vein grafts
RESTORE (9)	Tirofiban	2141	High risk PCI -acute MI or unstable angina within 72 hours

Randomized clinical trials in stent patients have evaluated the efficacy of both abciximab and eptifibatide compared with placebo (7,10). These studies show a statistically significant advantage of the GPIIb/IIIa inhibitor compared with placebo in decreasing the incidence of the combined endpoint of death, MI and urgent target vessel revascularization. Comparison of agents within the class is difficult due to differences in study design. The EPISTENT trial showed an absolute reduction in risk of death or MI at 30 days of 5.4%, compared with a 3.9% absolute risk reduction in ESPRIT (7,10). Also, abciximab's benefit is maintained out to one year in EPISTENT, but follow-up beyond 6 months is not yet available for ESPRIT.

Important differences between these two studies include the types of patients enrolled and differences in study design. For example, over half of patients in EPISTENT had an acute coronary syndrome or an acute MI within seven days of study enrollment compared with less than 20% of patients in ESPRIT (7,10). In addition, in ESPRIT cross-over to active treatment was allowed. Eptifibatide treatment significantly reduced the need for open-label "bail out" GPIIb/IIIa therapy in patients randomized to placebo which could have attenuated the absolute risk reduction seen between the groups (10). In addition, since these studies were conducted almost two years apart, several changes in interventional practice may have influenced outcomes. For example, in EPISTENT only one type of stent was used, as was the practice at the time (7). This stent had several limitations and could not be deployed in smaller vessels or vessels with substantial tortuosity, thus limiting our ability to extrapolate these results to contemporary interventional practice. In contrast, over twenty different FDA approved stents were deployed in the ESPRIT trial (10). Also, in ESPRIT, 96% of patients were pretreated with clopidogrel, as is now the standard of care. In the EPISTENT, pretreatment with ticlopidine was done at the investigator's discretion, and less than 60% of patients were pretreated (55). The absolute risk reduction in the primary endpoint in patients pretreated with ticlopidine in the abciximab study was 3.7% (8.9% stent+placebo, 5.2% stent+abciximab; $p=0.028$), similar to the absolute risk reduction seen in the ESPRIT trial (10,55).

Tirofiban was recently compared with abciximab in patients undergoing either elective or urgent angioplasty with stent placement in the TARGET trial (56). In this double-blind, double-dummy trial, patients were randomized to receive either tirofiban (10 mcg/kg bolus followed by a 0.15 mcg/kg infusion for 18-24 hours) or abciximab (0.25 mg/kg bolus followed by a 0.125 mcg/kg/min infusion for 12 hours). All patients received aspirin and clopidogrel loading (300 mg) at the time of stent placement was highly encouraged (>90% of patients received clopidogrel). All patients received 70 U/kg of heparin during the procedure. The primary endpoint of death, MI, and urgent target vessel revascularization occurred in significantly more patients randomized to tirofiban compared with abciximab (7.6% vs. 6.0%, $p=0.038$). The benefit of abciximab was seen early in the treatment period, and most events occurred while the drugs were infusing.

Combination Regimens

Notably, all patients undergoing PCI will receive aspirin therapy preferably before the procedure and then chronically thereafter (11). All contemporary PCI trials are conducted on a background of aspirin therapy. The following sections detail specific concerns regarding combination therapy with other anti-platelet agents and/or UFH.

Unfractionated Heparin and Platelet Glycoprotein IIb/IIIa Inhibitors

Administration of abciximab in conjunction with UFH increases the ACT by approximately 30-50s (57,58). In addition, it was found in the EPIC trial that as the dose of UFH (and the ACT) increased in patients who received abciximab, the rate of bleeding increased. For patients receiving 70 U/kg of UFH, the odds ratio for major bleeding risk was 1.22 (95% CI 0.28-5.38), for patients receiving 70-120 U/kg, the odds ratio for major bleeding was 3.75 (95% CI 1.2-11.75), while for patients receiving >120 U/kg, the odds ratio was 3.88 (95% CI 2.15-7.0). At the same time, there was no effect on the rate of periprocedural ischemic events (59). This observation prompted the initiation of the PROLOG and EPILOG studies which established that in patients receiving abciximab, reduction of the UFH dose from 100 U/kg to 70 U/kg lowered the rates of hemorrhage (non CABG-related major bleeding 1.9% vs. 1.1%, $p=NS$; minor bleeding 7.6% vs. 4.0%, $p<0.001$), and possibly reduced the rates of ischemic complications as well (5.4% vs. 5.2%, $p=NS$) (5,60). In EPILOG, median ACT values were 283 s in patients assigned to low dose weight adjusted UFH and 361 sec in patients assigned to receive 100 U/kg of UFH. Current ACCP guidelines recommend the using 70 IU/kg of UFH to reach a target ACT of >200 s with either the HemoTec or Hemochron device. Although there are sporadic case reports of even lower UFH doses being used in conjunction with abciximab, there are no systematically collected and assessed data to support a further reduction.

Data regarding the effect of the small molecule GPIIb/IIIa inhibitor's on ACT is less clear, although both are thought to prolong the ACT and therefore patients receiving these agents should receive 70 IU/kg of heparin to achieve an ACT of > 200 s as with abciximab (11). In the recently completed ESPRIT trial of high dose eptifibatide during PCI, all patients received 60 U/kg of UFH (10). In this study, as in EPIC, no relationship between ACT and the frequency of ischemic events was observed in patients assigned to receive the GPIIb/IIIa inhibitor and the bleeding rates were low in both groups. In the recently completed TARGET trial, mean maximum ACT were virtually identical after 70 IU/kg of UFH in patients randomized to either tirofiban or abciximab (281 s vs. 282 s, respectively) (56).

Thienopyridines and Glycoprotein IIb/IIIa Inhibitors

As yet, no clinical trial has evaluated the efficacy and safety of combination thienopyridine and a GPIIb/IIIa inhibitor compared with a GPIIb/IIIa inhibitor alone in patients receiving stents. In addition, there is no systematic evaluation of the safety and efficacy of loading doses of clopidogrel in patients receiving a GPIIb/IIIa inhibitor, only observational data from ESPRIT and TARGET (10,56). In both of these trials, clopidogrel 300 mg at the time of PCI was highly encouraged, but not mandated by the protocols. In addition, in all clinical trials that used a combination of ticlopidine or clopidogrel (with or without loading) and a GPIIb/IIIa inhibitor, overall hemorrhagic complications have been low. However, the numbers of patients not receiving a thienopyridine are too small to allow for comparisons between groups.

Safety Issues

Hemorrhagic complications in patients undergoing PCI remain a major challenge despite improvements in interventional procedural techniques and progress in the management of the arterial access site. Typically, any intracranial hemorrhage (ICH) or retroperitoneal hemorrhage, need for a blood transfusion or overt blood loss associated with a fall in hemoglobin concentration $>3\text{g/dL}$ or $>5\text{g/dL}$ are considered clinically significant and have been utilized in many PCI trials to define major bleeding complications (62). The rates of clinically significant hemorrhage in major randomized trials in PCI are summarized in Table IV. The incidence of hemorrhagic events in clinical trials varies widely. More recent trials using lower doses of heparin, smaller sheath sizes and early sheath removal have tended to report a lower incidence of hemorrhagic events.

The incidence of blood transfusions is an alternative measure of clinically important bleeding (62). Although this measure is influenced by differences in patient management, it may be the best available index of hemorrhagic events associated with PCI outside of clinical trials. Lauer et al, who studied a nationally representative sample of 37,088 patients undergoing PCI, reported a transfusion rate declining from 7.7% to 5.5% between 1995 and 1997 (63). The estimated additional cost of care for a patient receiving a transfusion was \$10,225 (95% CI $\pm$ \$300). In a smaller, single center study, Moscucci and others reported an incidence of blood transfusion of 8.9% among 628 consecutive patients undergoing PCI, but also concluded that 64% of these were given inappropriately when assessed according to published guidelines (64). Transfusion rates reported in the randomized trials cited in Table 4 have ranged widely between 0.6% (EPILOG) and 7.8% (EPIC). In general, transfusion rates in clinical trials have been lower than those observed in observational series of patients.

Table IV. Incidence of Clinically Significant Bleeding Associated with Glycoprotein IIb/IIIa Inhibitors in Patients Undergoing Percutaneous Coronary Intervention.

Study	Patients	Randomized Group	Size (n)	Incidence (%) of Clinically Significant Bleeding	
				$\geq 5\text{g/dL}$	$\geq 3\text{g/dL}$
CAPTURE (6)	Refractory/acute unstable angina	Heparin Abciximab	635	1.9	2.0
			630	3.8	4.8
EPIC (4)	High risk of abrupt vessel closure	Heparin Abciximab-bolus + infusion	696	3.3	9.2
			708	10.6	16.8
EPILOG (5)	Elective or urgent revascularization	Heparin	939	1.1	3.4
		Abciximab + low dose heparin	935	1.1	4.0
		Abciximab + std. dose heparin	918	1.9	7.6

EPISTENT (7)	Elective or urgent revascularization	Heparin + ticlopidine +stent	809	2.2	1.7
		Heparin + abciximab + iclopidine + stent	794	1.5	2.9
		Heparin + abciximab + balloon	796	1.4	2.9
IMPACT II (8)	Elective or urgent revascularization	Heparin	1285	4.5	9.3
		Eptifibatide 135/0.5	1300	4.4	11.7
		Eptifibatide 135/0.75	1286	4.7	14.2
RAPPORT (65)	PCI for acute myocardial infarction	Heparin	242	9.5	Data not reported
		Abciximab	241	16.6	
RESTORE (9)	Unstable angina or AMI	Heparin	1070	1.6	6.3
		Heparin + tirofiban	1071	2.2	12.0
ESPRIT (10)	Planned elective stent PCI	Heparin + clopidogrel	1024	0.4	2.2
		Heparin + eptifibatide + clopidogrel	1040	1.4	4.2
TARGET (56)	Elective or urgent stent PCI	Heparin + abciximab + clopidogrel	2414	0.95	5.6
		Heparin + tirofiban + clopidogrel	2398	1.2	3.5

Summary

Major advances in PCI have occurred since this procedure was first introduced. Adjunctive pharmacologic therapy both during and after PCI is a key factor in the continued success of PCI. As we continue to advance our knowledge in this area and offer PCI to more and more patients, we must address the dilemma of how to construct more potent combinations of anticoagulant and antiplatelet agents, affording greater protection against ischemic complications, without increasing the risk of bleeding.

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The Role of Anticoagulant and Antiplatelet Therapy in Percutaneous Coronary Intervention

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Background: Unfractionated heparin (UFH) has traditionally been the anticoagulant of choice for prevention of thrombus formation during percutaneous coronary intervention (PCI). However, in the past several years, newer anticoagulants such as the intravenous platelet glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors were found to be important adjunctive therapy in PCI for reduction of death and non-fatal myocardial infarction. In addition, patients receiving an intracoronary stent have been shown to benefit from oral anti-platelet therapy with aspirin plus a thienopyridine for 2-4 weeks after the procedure.

Methods: A MEDLINE search (July 1966 - May 2001) was conducted to identify all publications evaluating the use of anticoagulant or antiplatelet agents during PCI. When available, randomized clinical trials were included. Some case-controlled and retrospective evaluations are included due to lack of randomized clinical trial data of certain agents.

Results: The appropriate intensity of anticoagulation with UFH is controversial. Low-molecular weight heparins or direct thrombin inhibitors may offer a better alternative to UFH in PCI in the future. Introduction of potent platelet inhibitors have increased the success of PCI, but at the expense of an increased bleeding complications. The impact of multiple anticoagulant and antiplatelet regimens on bleeding complications is unknown, especially in older, more debilitated populations.

Conclusions: Adjuvant antiplatelet and antithrombotic therapy are essential to improve ischemic outcomes after PCI. The challenge in the next few years will be to develop agents and dosing schemes that better balance the benefit of decreased ischemic complications with bleeding adverse effects.

J Inform Pharmacother 2001;6:300-313.

Non-surgical revascularization of coronary arteries narrowed by atherosclerosis was first performed in 1977 (1). In recent years, percutaneous transluminal coronary angioplasty (PTCA) has been supplemented with other non-surgical revascularization techniques including directional atherectomy, rotational atherectomy and coronary stenting. The term percutaneous coronary intervention (PCI) has been introduced to encompass all of these procedures.

Although PCI is generally safe, complications can occur including myocardial infarction (2.8%) and death (2%) (2). Dilatation of a stenotic coronary artery causes plaque rupture and exposure of the sub-endothelium (3). These events are powerful stimuli for activation of the coagulation cascade and aggregation of platelets. Fatal and non-fatal myocardial infarction (MI) are typically caused by platelet aggregation and thrombus formation at the site of vessel injury, platelet microemboli formation that occludes smaller vessels downstream, or both (3). Unfractionated heparin (UFH) has traditionally been the anticoagulant of choice for prevention of thrombus formation during PCI (1). However, in the past several years, newer anticoagulants such as the intravenous platelet glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors were found to be important adjunctive therapy in PCI for reduction of death and non-fatal MI (4-10).

Recent data indicates that as many as 70% of all patients undergoing a percutaneous intervention will receive a coronary stent (2). Stenting has clearly been effective in decreasing the need for repeat interventions, but the risk of precipitating thrombosis and distal thrombus embolization downstream from the stent are thought to be problematic (2). Acute administration of potent anti-platelet agents are thought to prevent early thrombotic occlusion of the stent, and concomitant oral anti-platelet therapy with aspirin and a thienopyridine for 2-4 weeks after the procedure has been shown to decrease the incidence

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of delayed or sub-acute stent thrombosis (occurring 2 to 30 days after the procedure) (11).

Although this multi-pronged approach appears to be effective in decreasing the thrombus formation and the subsequent risk of MI, this benefit needs to be balanced against the real risk of increased bleeding events. The challenge in the next several years will be in determining how to safely use these agents in combination, and in developing agents that provide protection against thrombosis and MI without increasing the risk for adverse bleeding events. The purpose of this review is to outline the history of anticoagulation and antiplatelet therapy in PCI, to discuss the evidence for the efficacy and safety of these agents in this setting, and to discuss new pharmacologic developments that hold promise in this area.

The Role of Unfractionated Heparin in Percutaneous Coronary Interventions

Data from a variety of preclinical and clinical trials indicate that anti-thrombin treatment is a necessary adjunct for PCI (12-15). The clinical need for anti-thrombin treatment is reinforced by data from diagnostic cardiac catheterization showing 50% reductions in death and MI among 125,000 patients treated with UFH compared to 125,000 with no UFH (16). Thrombin plays a crucial role in the cascade of reactions leading to thrombus formation at the site of endothelial injury. In addition, thrombin is involved in post-thrombotic events such as attraction of inflammatory cells and the regulation of growth of endothelial and vascular smooth muscle cells (17). Nevertheless, ideal dosing and monitoring of UFH during PCI remains controversial.

Unfractionated Heparin Monitoring

Although the activated partial thromboplastin time (aPTT) is traditionally used to measure the intensity of UFH anticoagulation, the need for a point of care measurement device makes the activated clotting time (ACT) the preferred monitoring parameter for UFH therapy during PCI. In addition, ACT values are linearly related to UFH levels, whereas aPTT levels become unmeasurable when high UFH concentrations

are achieved as is the case during PCI (18). Two commercially available point-of-care monitoring devices for ACT are widely used; the HemoTec (HemoTec Inc, Englewood, CO) and Hemochron (International Technidyne Corporation, Edison, NJ) devices. The Hemochron device gives values 30-50 seconds (s) higher than the HemoTec at all UFH concentrations (19).

Early recommendations for ACT-guided monitoring of UFH dose during PCI came from the cardiopulmonary bypass literature and were based on observations that thrombosis occurred on membrane oxygenators found in cardiopulmonary bypass circuits at ACT values less than 300 s (20). In non-human primate experiments, fibrin monomer can be detected in the bypass circuit at ACT values below 400 s (21). Consequently, an ACT value between 300 s and 400 s has been proposed as a threshold for anticoagulation during PCI. Current guidelines promoted by the American College of Chest Physicians (ACCP) recommend using a target ACT value of 250 s to 300 s with the HemoTec device and 300 s to 350 s with the Hemochron device (11). However, most studies investigating the effects of peri-procedural UFH intensity on angiographic and clinical outcomes have been retrospective and nonrandomized. As a result, the efficacy of anticoagulation when the ACT is maintained at these values remains controversial.

Case Control Studies

A case-control study evaluated 186 subjects from a series of 1290 patients undergoing non-emergent angioplasty (13). Hemochron ACTs in 62 patients who experienced ischemic complications after angioplasty (cases) were compared to 124 matched patients without complications (controls). All patients received aspirin and 10,000 U of UFH as a bolus prior to PCI. Adverse clinical outcomes were defined as death, MI, or need for urgent revascularization. Relative to the control population, patients who experienced adverse clinical outcomes had significantly lower initial and minimum ACTs. The odds ratio for adverse outcomes among patients with ACT ≥ 300 s compared with ACT <300 s was 0.34 (95% confidence interval [CI], 0.15 to 0.77).

Ferguson et al. reviewed 1469 consecutive PTCA procedures performed at a single center using a case-

control analysis (14). Activated clotting times of 103 patients with major in-hospital complications (cases) were compared to 400 randomly selected, matched, uncomplicated patients from the same series (controls). All patients had ACTs measured at baseline, after UFH therapy, and at the end of the procedure. There were no differences in baseline ACTs between the two groups. Adverse clinical outcomes included death and urgent or emergent bypass surgery. Patients with subsequent complications had significantly lower ACTs after UFH therapy and at the end of the procedure. There were 63/103 cases with initial HemoTec ACT < 250 seconds, and 108/400 control patients with ACT < 250 seconds. The odds ratio for adverse outcomes was 0.23 (95% CI, 0.15 to 0.37).

McGarry et al. analyzed 487 consecutive patients who underwent elective angioplasty at single center (8). A total of 336 patients had documented aPTT. Patients were divided into two groups: those with aPTT ≥ 3 times the control value ($n=271$), and those with aPTT < 3 times the control value ($n=65$). Blood samples were obtained after the procedure and before discontinuation of UFH for sheath removal. Clinical outcomes included death and ischemic complications (chest pain with > 1 mm ST segment elevation in the dilated territory associated with elevation in creatine kinase MB fraction) prior to hospital discharge. There was a statistically significant reduction in the incidence of ischemic events (1.5% vs. 9.2%, $p < 0.001$) in patients with aPTT values ≥ 3 times the control value at hospital discharge. There were 7 complications in the 65 patients with PTT < 3 times the control value, and 7 complications in the 271 patients with PTT ≥ 3 times the control value. The odds ratio for adverse outcomes was 0.22 (95% CI, 0.08 to 0.65).

Randomized Trials

Unfractionated heparin dosing for anticoagulation during elective PCI has been compared in two small, randomized trials. Vainer et al. randomized a total of 404 patients with stable angina undergoing PCI to receive either 5000 units (205 patients) or 20,000 units (199 patients) of UFH intravenously as a bolus prior to the procedure (22). The mean ACT was 209 ± 69 s for low dose and 381 ± 117 s for high dose patients measured by the HemoTec device. The

composite endpoint of death, MI, repeat PCI or acute occlusion was observed in 27/204 patients (13.2%) receiving low dose UFH and in 16/199 patients (8.0%) receiving high dose UFH (odds ratio [OR] 1.74; 95% CI 0.91-3.35).

Boccaro et al. randomized 400 patients to high fixed dose UFH bolus (15,000 U) or a weight-adjusted UFH (100 U/kg) (23). Additional UFH bolus doses were administered if the procedure lasted more than one hour or at the discretion of the operator if complications appeared. Patients were monitored using aPTT. Clinical endpoints were defined as death, Q- or non-Q wave MI, unplanned repeat PTCA, CABG or bailout stenting, and major hemorrhage. The average total UFH dose actually received was $15,300 \pm 888$ U in the high fixed dose group and 8251 ± 2027 U in the weight-adjusted group, corresponding to doses of 208 ± 41 and 110 ± 22 U/kg body weight respectively. Stents were placed in 28.5% and 26.5% of patients respectively. The primary endpoint (freedom from death, myocardial infarction, unplanned revascularization or bailout stenting) occurred in 91% and 95% of patients in the high-fixed and low-weight adjusted dose groups respectively (OR 1.88; 95% CI 0.80-4.50, $p = 0.12$).

Post-procedural Unfractionated Heparin

Two studies have evaluated the utility of post-procedural intravenous UFH after uncomplicated PCI (24,25). Both found that serious bleeding complications were increased. Evaluation of serious bleeding complications between post-procedural subcutaneous UFH and intravenous UFH was compared in another trial. Bleeding rates were significantly lower in the group receiving subcutaneous UFH, but ischemic complications were similar between the two groups (26). Due to the potential to increase the risk of serious bleeding complications, routine post-procedural UFH infusions are not recommended for uncomplicated PCI.

Alternatives to Unfractionated Heparin in Percutaneous Coronary Interventions

Newer developments such as the use of low-molecular-weight derivatives of UFH and direct

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antagonists of thrombin may be useful in improving the safety and efficacy of anticoagulation during interventional procedures.

Low-Molecular-Weight Heparins

The low-molecular-weight heparins (LMWH) are produced by enzymatic or chemical degradation of UFH, and consist of smaller polysaccharide chains with higher ratios of anti-Xa:anti-IIa activity than UFH (27). Low-molecular-weight heparins have become increasingly popular within the last several years, in large part as a consequence of their ease of use as well as two trials indicating possible superiority of enoxaparin compared with UFH in patients presenting with non-ST-segment elevation acute coronary syndromes (NSTEMI ACS) (28,29).

At present, experience with LMWH in PCI consists of three safety registries and a small, randomized trial. The one randomized trial, Reduction of Restenosis After PTCA, Early Administration of Reviparin in a Double-Blind, Unfractionated Heparin and Placebo-Controlled Evaluation (REDUCE) was performed in 1993 and 1994 (30). In this trial, the LMWH reviparin (7,000 U bolus followed by infusion and subcutaneous injection) was compared with UFH (10,500 U bolus followed by infusion) in 612 patients. Platelet glycoprotein IIb/IIIa receptor antagonists were not used and stents were implanted only for abrupt closure. The primary endpoint, a composite of ischemic events at six months was not different between the two groups; however in the reviparin-treated group, the rate of rescue stent implantation on the day of the PCI was reduced from 6.9% to 2%. Three safety registries evaluated the use of enoxaparin in PCI have been developed. The National Investigators Collaborating on Enoxaparin (NICE) group recently published results of the NICE-1 and NICE-4 studies, and the NICE-3 data was discussed at the Transcatheter Therapeutics Conference in 2000 (31-33). In the NICE-1 registry, patients received enoxaparin 1.0 mg/kg as an intravenous bolus prior to PCI (30). In the NICE-4 registry, patients received 0.75 mg/kg of intravenous enoxaparin in addition to traditional doses of abciximab (31). Within these studies, levels of anti-Xa activity were similar to levels that have been reported in patients treated with a 10,000 U bolus of UFH (37,38). In the NICE-3 registry, the safety of enoxaparin 1 mg/kg

subcutaneously in combination with all three GPIIb/IIIa inhibitors were evaluated in 616 patients with NSTEMI ACS (31). In this evaluation, 292 patients underwent PCI and received no UFH. If the PCI was performed <8 hours after the enoxaparin administration, no additional anticoagulation was used. If the PCI was performed >8 hours after enoxaparin administration, 0.3 mg/kg of enoxaparin was given intravenously (32). Observations from all registries appear promising in that the rates of bleeding were similar compared with historical controls (Table I). It should be noted that these trials were observational and designed to evaluate safety, not efficacy endpoints. These preliminary investigations should be a firm foundation for the design of large-scale randomized trials in the future that will be powered to detect efficacy differences.

Direct Thrombin Inhibitors

The development of direct thrombin inhibitors has been based on the characterization of hirudin, a 65-amino acid polypeptide isolated from the salivary gland of the medicinal leech that is a potent irreversible inhibitor of thrombin. Hirudin binds to thrombin at the catalytic site and also at the anion binding exosite by an anionic hirudin tail fragment (33). Commercially available direct thrombin inhibitors include argatroban, lepirudin, and bivalirudin.

Argatroban is a synthetic direct thrombin inhibitor derived from L-arginine indicated for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT) (34). Unlike bivalirudin and lepirudin, argatroban is eliminated hepatically rather than renally. Pilot studies using it in PCI patients with and without HIT indicate that it may be safe and effective. Larger, randomized trials need to be performed to determine safety, efficacy and an optimal dosing regime.

Lepirudin is a recombinant hirudin derivative which binds specifically and irreversibly to thrombin. Approximately 50% of the drug is eliminated renally, so the dose should be adjusted in patients with significant renal impairment. Similar to argatroban, some case reports have been published using lepirudin in PCI in patients with HIT, but little other data are available (35).

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Table I. Summary of Safety Findings from Low-Molecular-Weight Heparin Registries

Study	Treatment	Frequency of Clinically Significant Bleeds (%)	
		Major CABG	Major Non-CABG
NICE-1 (30)	Enoxaparin 1mg/kg	1.1	0.5
NICE -3 (32)	Enoxaparin 1mg/kg	6.7	4.4
	+tirofiban	5.1	1.4
	+eptifibatide	4.4	3.2
	+abciximab	4.1	0.7
NICE-4 (31)	Enoxaparin 0.75 mg/kg + abciximab	0.4	0.2

Bivalirudin is a synthetic peptide derivative of hirudin with unique thrombin binding characteristics. Initially, bivalirudin binding is non-competitive and complete. However, thrombin recognizes bivalirudin as a substrate and cleaves the D-Phe-Phe-Arg-Pro moiety of bivalirudin, thereby freeing the active binding site of thrombin once again. This vacates thrombin's active site and leaves in place the bivalirudin moiety binding competitively to thrombin's fibrin binding site. In this configuration, thrombin is able to recognize other competing substrates and participate in the coagulation process to maintain hemostasis (36). Bivalirudin is currently the only direct thrombin inhibitor indicated for replacing UFH during PCI by the United States Food and Drug Administration.

In a multi-center trial, 4,312 patients with severe, accelerating or rest angina within the last month and suitable coronary-artery lesions were randomly treated with UFH (n=2151), or bivalirudin (n=2161) and PCI (37,38). The primary endpoint was defined as a combination of death, MI (enzymatically or clinically defined), or the need for repeat revascularization in the first 7-days, with specified follow-up at 90-days and 6-months. The combined clinical endpoint occurred in 7.9% of patients in the UFH group, and in 6.2% of patients in the bivalirudin group (OR 0.78; 95% CI 0.62-0.99 p=0.039). Absolute differences were maintained at 90-days (p=0.012), but were no longer statistically significant at 6-months (p=0.15). Among a pre-stratified and separately randomized group of 741 patients with post-MI unstable angina, the combined clinical endpoint occurred in 37 (9.9%) of 372 patients in the UFH group, and in 18 (4.9%) of 369 patients in the bivalirudin group (OR 0.47; 95% CI 0.26-0.84 p=0.009). Differences were maintained out

to 30 days (p=0.003) and 6 months (p=0.049). Clinically significant bleeding complications occurred in 9.3% of patients in the UFH group and 3.5% of patients in the bivalirudin group (OR 0.34; 95% CI 0.26-0.45, p<0.001). The reduction in bleeding complications was driven by lower transfusion rates (p<0.001) and lower major bleeds associated with $\geq 5\text{g/dl}$ decrease in hemoglobin concentration (p<0.001) among patients assigned bivalirudin (37). The main limitations of this trial are that it was performed in the early 1990's, prior to the introduction and widespread use of stents and GPIIb/IIIa inhibitors. In addition, the initial dose of UFH during PCI was much higher than currently utilized doses (175 u/kg), and post-procedural UFH was prescribed for 18-24 hours per protocol which could have lead to a higher incidence of bleeding complications in the UFH group. Ongoing trials are currently investigating the safety and efficacy of bivalirudin in contemporary interventional cardiology practice (39,40).

The Role of Anti-platelet Agents in Percutaneous Coronary Interventions

Percutaneous coronary intervention is complicated by platelet activation which may lead to adverse events after these procedures. Administration of aspirin reduces complications of ischemia after PCI, although the minimum effective aspirin dosage is unknown (11). One study of low-dose (80 mg/day) compared with high dose (1500 mg/day) aspirin found no difference in MI or the need for coronary artery bypass surgery (41). Since higher doses can be associated with gastrointestinal irritations, lower empiric doses (80-325 mg daily) are recommended in PCI (11). When possible, it is probably prudent to

administer aspirin at least 2 hours prior to the procedure (11). Although other agents also prevent early complications after angioplasty, none has been shown to be superior to aspirin (42, 43).

Thienopyridines

The thienopyridines, ticlopidine and clopidogrel, inhibit platelet aggregation induced by adenosine diphosphate (ADP) (44). Thienopyridines have been shown to improve outcomes when given in addition to aspirin in patients undergoing stent placement (45). Due to a perceived superior safety profile, clopidogrel has become the thienopyridine of choice for the prevention of stent thrombosis (46). Most of the data demonstrating a benefit of clopidogrel in patients with stents are in case-series or retrospective analysis using historical ticlopidine controls (Table II) (47-49). However, two randomized trials were recently published which confirm results from these smaller single-center studies (46,50).

One trial compared the safety of four weeks of ticlopidine 500 mg/day (n=345) to clopidogrel 75 mg/day (n=355) after successful stenting during elective or emergency PCI (50). All patients also received 100 mg of aspirin daily. They found no difference in the primary cardiac endpoint (cardiac death, urgent target vessel revascularization, angiographically determined thrombotic stent occlusions or non-fatal MI) within 30 days, but the trial was not powered to detect differences in efficacy. Cardiac events occurred in 11 patients taking clopidogrel (3.1%) and in 6 patients taking ticlopidine (1.7%). The primary noncardiac endpoint (death from noncardiac cause, severe hemorrhagic event, or adverse event causing discontinuation of study medication) occurred in 16 patients on clopidogrel (4.5%) compared with 33 patients assigned to ticlopidine (9.6%). Of note, this trial did not use the popular "loading dose" of clopidogrel which is commonly used in clinical practice.

In the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS) trial, 1020 patients were randomized after successful coronary stenting to a 28-day course of clopidogrel 75 mg daily with or without a 300 mg loading dose, or to 250 mg of ticlopidine twice daily (46). The primary endpoint of major peripheral bleeding complications,

neutropenia, thrombocytopenia, or early discontinuation of study drug as the result of noncardiac adverse events was reached in 9.1% of patients on ticlopidine compared with 4.6% of patients on the combined clopidogrel regimens (RR 0.5; 95% CI 0.31 to 0.81; p=0.005). Overall rates of major adverse cardiac events were low and did not differ significantly between the three groups (0.9% with ticlopidine, 1.5% with 75 mg/d clopidogrel, 1.2% with clopidogrel loading, p=NS). Notably, the CLASSICS trial excluded patients undergoing PCI for primary angioplasty, patients whose baseline cardiac enzymes were greater than twice the upper limit of normal, those requiring a GPIIb/IIIa inhibitor, on oral anticoagulants and those who received a thrombolytic agent within 2 weeks prior to the procedure. In addition, patients requiring placement of more than two stents or stenting to more than one vessel were also excluded.

Neither of these trials were powered to detect differences in cardiac event rates, but ticlopidine consistently had lower event rates compared with clopidogrel. Nevertheless, because of its superior safety profile demonstrated in these two reports, clopidogrel is now considered the preferred thienopyridine in patients undergoing stent placement.

Phosphodiesterase Inhibitors

Cilostazol is an antiplatelet agent that increases the intracellular cyclic adenosine monophosphate concentrations by inhibiting phosphodiesterase III. Most research using cilostazol in PCI has focused on its effects on reducing the phenomena of restenosis (51). Restenosis is an abnormal type of vascular remodeling where smooth muscle cells proliferate in the intima of the artery resulting in reocclusion and the need for repeat interventions. In addition to its antiplatelet effects and inhibition of smooth muscle cell proliferation, cilostazol is thought to enhance reendothelialization after PCI (51). Enhanced regeneration of the endothelium after stent placement would decrease the thrombogenicity of the stent, possibly decreasing cardiac events that may occur as a result of stent thrombosis. In one study, 409 patients were randomized to receive aspirin plus ticlopidine or aspirin plus cilostazol started two days prior to elective stent placement. Ticlopidine (250

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Table II. Summary of Non-Randomized Observational Reports of the Safety and Efficacy of Clopidogrel in Patients Undergoing Stent Placement.

Study	Design	Regimen	Size (n)	Outcomes	Results
Berger (48)	Observational, consecutive stent placement	Clopidogrel 300 mg once then 75 mg/day for 2 weeks $\pm$ abciximab	500	30 day combined endpoint of death, nonfatal MI, stent thrombosis and need for repeat revascularization or CABG	Death=0.4% MI=0.0% Revasc=0.4%
Moussa (47)	Retrospective, observational, successful stent placement on no GPIIb/IIIa	Ticlopidine 500mg once then 250 mg bid for 2 weeks or	1406	30 day death, MI, stent thrombosis, CABG, adverse drug reactions (ADRs)	Death=0.9% (T) vs. 1.0% (C) MI=1.8% (T) vs. 0.7% (C) Stent thrombosis=1.5% (T) vs. 1.4% (C) CABG=0.4% (T) vs. 0.7% (C) ADRs=10.6% (T) vs. 5.3% (C)
		Clopidogrel 300 mg once then 75 mg/d for 4 weeks	283		
Mishkel (49)	Consecutive stent placement	Clopidogrel 75 mg/d or	514	30 day death, MI, stent thrombosis, urgent revascularization	Death=0.6% (T) vs. 0.9% (C) MI=0.6% (T) vs. 1.0% (C) Revasc=0.3% (T) vs. 0.6% (C)
		Ticlopidine 250 mg bid at the operators discretion	361		

mg twice daily) was given for one month post-stent placement, and cilostazol (200 mg twice daily) for six months post-stent placement. Follow-up angiography was performed at six months on 77% of patients. No cases of stent thrombosis were reported, and the restenosis rate was 27% in the ticlopidine group compared with 23% in the cilostazol group ($p=NS$) (52). However, diffuse type in-stent restenosis was significantly reduced by cilostazol (54% vs. 27%, $p<0.05$). In diabetic patients, restenosis was also significantly reduced by cilostazol (50% vs. 22%, $p<0.05$). Clinical events did not differ between the two groups.

Another study aimed to evaluate the efficacy of cilostazol for prevention of stent thrombosis. Four hundred and ninety patients were randomized to receive aspirin plus ticlopidine (250 mg twice daily) or aspirin plus cilostazol (200 mg twice daily) for one month. Major cardiac events were similar at 30 days in the two groups (2.9% vs. 1.6%, respectively). However this study was not powered to detect differences in clinical event rates. Withdrawal from

therapy due to an adverse drug reaction occurred in 2.9% of patients on ticlopidine and 2.0% of patients on cilostazol ($p=NS$) (53).

Glycoprotein IIb/IIIa Inhibitors

Platelet aggregation is dependent on activation of the GPIIb/IIIa receptor, the final common pathway of platelet activation (54). The GPIIb/IIIa receptor is necessary for platelet binding to fibrinogen, which leads to subsequent formation of a platelet plug and eventually to an intracoronary thrombus if left unchecked. Inhibition of platelet activation using aspirin and UFH provides some benefit in PCI, but does not always insure optimal outcomes due to insufficient platelet inhibition. Specific inhibitors of the GPIIb/IIIa receptor used together with UFH, have been shown to improve outcomes of patients undergoing PCI compared with UFH alone (Table III) (4-10).

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Table III. Summary of Placebo-controlled Glycoprotein IIb/IIIa Inhibitor Trials in Patients Undergoing Percutaneous Coronary Intervention.

Study	Agent	Patients (n)	Patient Population
EPIC (4)	Abciximab	2099	High risk PCI -MI within 12 hours -MI within 7 days -chest pain within 24 hours
EPILOG (5)	Abciximab	2792	Urgent or elective PCI -excluding unstable angina or MI within 24 hours
CAPTURE (6)	Abciximab	1265	Refractory unstable angina undergoing PCI -chest pain within 48 hours despite therapy with nitrates and intravenous UFH
RAPPORT (65)	Abciximab	483	STEMI within 12 hours
EPISTENT (7)	Abciximab	2399	Elective or urgent PCI with or without stent placement
ADMIRAL (66)	Abciximab	300	STEMI within 12 hours
CADILLAC (67)	Abciximab	2082	STEMI within 12 hours -excluding high risk anatomy, Killip Class IV
IMPACT II (8)	Eptifibatide	4010	All PCI
ESPRIT (10)	Eptifibatide	2064	Elective (non-urgent) PCI with stent placement -excluding saphenous vein grafts
RESTORE (9)	Tirofiban	2141	High risk PCI -acute MI or unstable angina within 72 hours

Randomized clinical trials in stent patients have evaluated the efficacy of both abciximab and eptifibatide compared with placebo (7,10). These studies show a statistically significant advantage of the GPIIb/IIIa inhibitor compared with placebo in decreasing the incidence of the combined endpoint of death, MI and urgent target vessel revascularization. Comparison of agents within the class is difficult due to differences in study design. The EPISTENT trial showed an absolute reduction in risk of death or MI at 30 days of 5.4%, compared with a 3.9% absolute risk reduction in ESPRIT (7,10). Also, abciximab's benefit is maintained out to one year in EPISTENT, but follow-up beyond 6 months is not yet available for ESPRIT.

Important differences between these two studies include the types of patients enrolled and differences in study design. For example, over half of patients in EPISTENT had an acute coronary syndrome or an acute MI within seven days of study enrollment compared with less than 20% of patients in ESPRIT (7,10). In addition, in ESPRIT cross-over to active treatment was allowed. Eptifibatide treatment significantly reduced the need for open-label "bail out" GPIIb/IIIa therapy in patients randomized to placebo which could have attenuated the absolute risk reduction seen between

the groups (10). In addition, since these studies were conducted almost two years apart, several changes in interventional practice may have influenced outcomes. For example, in EPISTENT only one type of stent was used, as was the practice at the time (7). This stent had several limitations and could not be deployed in smaller vessels or vessels with substantial tortuosity, thus limiting our ability to extrapolate these results to contemporary interventional practice. In contrast, over twenty different FDA approved stents were deployed in the ESPRIT trial (10). Also, in ESPRIT, 96% of patients were pretreated with clopidogrel, as is now the standard of care. In the EPISTENT, pretreatment with ticlopidine was done at the investigator's discretion, and less than 60% of patients were pretreated (55). The absolute risk reduction in the primary endpoint in patients pretreated with ticlopidine in the abciximab study was 3.7% (8.9% stent+placebo, 5.2% stent+abciximab; $p=0.028$), similar to the absolute risk reduction seen in the ESPRIT trial (10,55).

Tirofiban was recently compared with abciximab in patients undergoing either elective or urgent angioplasty with stent placement in the TARGET trial (56). In this double-blind, double-dummy trial, patients were randomized to receive either tirofiban

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(10 mcg/kg bolus followed by a 0.15 mcg/kg infusion for 18-24 hours) or abciximab (0.25 mg/kg bolus followed by a 0.125 mcg/kg/min infusion for 12 hours). All patients received aspirin and clopidogrel loading (300 mg) at the time of stent placement was highly encouraged (>90% of patients received clopidogrel). All patients received 70 U/kg of heparin during the procedure. The primary endpoint of death, MI, and urgent target vessel revascularization occurred in significantly more patients randomized to tirofiban compared with abciximab (7.6% vs. 6.0%, $p=0.038$). The benefit of abciximab was seen early in the treatment period, and most events occurred while the drugs were infusing.

Combination Regimens

Notably, all patients undergoing PCI will receive aspirin therapy preferably before the procedure and then chronically thereafter (11). All contemporary PCI trials are conducted on a background of aspirin therapy. The following sections detail specific concerns regarding combination therapy with other anti-platelet agents and/or UFH.

Unfractionated Heparin and Platelet Glycoprotein IIb/IIIa Inhibitors

Administration of abciximab in conjunction with UFH increases the ACT by approximately 30-50s(57,58). In addition, it was found in the EPIC trial that as the dose of UFH (and the ACT) increased in patients who received abciximab, the rate of bleeding increased. For patients receiving 70 U/kg of UFH, the odds ratio for major bleeding risk was 1.22 (95% CI 0.28-5.38), for patients receiving 70-120 U/kg, the odds ratio for major bleeding was 3.75 (95% CI 1.2-11.75), while for patients receiving >120 U/kg, the odds ratio was 3.88 (95% CI 2.15-7.0). At the same time, there was no effect on the rate of periprocedural ischemic events (59). This observation prompted the initiation of the PROLOG and EPILOG studies which established that in patients receiving abciximab, reduction of the UFH dose from 100 U/kg to 70 U/kg lowered the rates of hemorrhage (non CABG-related major bleeding 1.9% vs. 1.1%, $p=NS$; minor bleeding 7.6% vs. 4.0%, $p<0.001$), and possibly reduced the rates of ischemic complications as well (5.4% vs. 5.2%, $p=NS$) (5,60). In EPILOG, median ACT values were 283 s in patients assigned to low dose

weight adjusted UFH and 361 sec in patients assigned to receive 100 U/kg of UFH. Current ACCP guidelines recommend the using 70 IU/kg of UFH to reach a target ACT of >200 s with either the HemoTec or Hemochron device. Although there are sporadic case reports of even lower UFH doses being used in conjunction with abciximab, there are no systematically collected and assessed data to support a further reduction.

Data regarding the effect of the small molecule GPIIb/IIIa inhibitor's on ACT is less clear, although both are thought to prolong the ACT and therefore patients receiving these agents should receive 70 IU/kg of heparin to achieve an ACT of > 200 s as with abciximab (11). In the recently completed ESPRIT trial of high dose eptifibatide during PCI, all patients received 60 U/kg of UFH (10). In this study, as in EPIC, no relationship between ACT and the frequency of ischemic events was observed in patients assigned to receive the GPIIb/IIIa inhibitor and the bleeding rates were low in both groups. In the recently completed TARGET trial, mean maximum ACT were virtually identical after 70 IU/kg of UFH in patients randomized to either tirofiban or abciximab (281 s vs. 282 s, respectively) (56).

Thienopyridines and Glycoprotein IIb/IIIa Inhibitors

As yet, no clinical trial has evaluated the efficacy and safety of combination thienopyridine and a GPIIb/IIIa inhibitor compared with a GPIIb/IIIa inhibitor alone in patients receiving stents. In addition, there is no systematic evaluation of the safety and efficacy of loading doses of clopidogrel in patients receiving a GPIIb/IIIa inhibitor, only observational data from ESPRIT and TARGET (10,56). In both of these trials, clopidogrel 300 mg at the time of PCI was highly encouraged, but not mandated by the protocols. In addition, in all clinical trials that used a combination of ticlopidine or clopidogrel (with or without loading) and a GPIIb/IIIa inhibitor, overall hemorrhagic complications have been low. However, the numbers of patients not receiving a thienopyridine are too small to allow for comparisons between groups.

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Table IV. Incidence of Clinically Significant Bleeding Associated with Glycoprotein IIb/IIIa Inhibitors in Patients Undergoing Percutaneous Coronary Intervention.

Study	Patients undergoing PCI	Randomized treatment group	Size (n)	Incidence (%) of clinically significant bleeding	
				$\geq 5\text{g/dL}$	$\geq 3\text{g/dL}$
CAPTURE (6)	Refractory/acute unstable angina	Heparin	635	1.9	2.0
		Abciximab	630	3.8	4.8
EPIC (4)	High risk of abrupt vessel closure	Heparin	696	3.3	9.2
		Abciximab-bolus + infusion	708	10.6	16.8
EPILOG (5)	Elective or urgent revascularization	Heparin	939	1.1	3.4
		Abciximab + low dose heparin	935	1.1	4.0
		Abciximab + std. dose heparin	918	1.9	7.6
EPISTENT (7)	Elective or urgent revascularization	Heparin + ticlopidine +stent	809	2.2	1.7
		Heparin + abciximab + Ticlopidine + stent	794	1.5	2.9
		Heparin + abciximab + balloon	796	1.4	2.9
IMPACT II (8)	Elective or urgent revascularization	Heparin	1285	4.5	9.3
		Eptifibatide 135/0.5	1300	4.4	11.7
		Eptifibatide 135/0.75	1286	4.7	14.2
RAPPORT (65)	PCI for acute myocardial infarction	Heparin	242	9.5	Data not reported
		Abciximab	241	16.6	
RESTORE (9)	Unstable angina or AMI	Heparin	1070	1.6	6.3
		Heparin + tirofiban	1071	2.2	12.0
ESPRIT (10)	Planned elective stent PCI	Heparin + clopidogrel	1024	0.4	2.2
		Heparin + eptifibatide + clopidogrel	1040	1.4	4.2
TARGET (56)	Elective or urgent stent PCI	Heparin + abciximab + clopidogrel	2414	0.95	5.6
		Heparin + tirofiban + clopidogrel	2398	1.2	3.5

Safety Issues

Hemorrhagic complications in patients undergoing PCI remain a major challenge despite improvements in interventional procedural techniques and progress in the management of the arterial access site. Typically, any intracranial hemorrhage (ICH) or retroperitoneal hemorrhage, need for a blood transfusion or overt blood loss associated with a fall in hemoglobin concentration $>3\text{g/dL}$ or $>5\text{g/dL}$ are considered clinically significant and have been utilized in many PCI trials to define major bleeding complications (62). The rates of clinically significant

hemorrhage in major randomized trials in PCI are summarized in Table IV. The incidence of hemorrhagic events in clinical trials varies widely. More recent trials using lower doses of heparin, smaller sheath sizes and early sheath removal have tended to report a lower incidence of hemorrhagic events.

The incidence of blood transfusions is an alternative measure of clinically important bleeding (62). Although this measure is influenced by differences in patient management, it may be the best available index of hemorrhagic events associated with PCI outside of clinical trials. Lauer et al, who

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studied a nationally representative sample of 37,088 patients undergoing PCI, reported a transfusion rate declining from 7.7% to 5.5% between 1995 and 1997 (63). The estimated additional cost of care for a patient receiving a transfusion was \$10,225 (95% CI $\pm$ \$300). In a smaller, single center study, Moscucci and others reported an incidence of blood transfusion of 8.9% among 628 consecutive patients undergoing PCI, but also concluded that 64% of these were given inappropriately when assessed according to published guidelines (64). Transfusion rates reported in the randomized trials cited in Table 4 have ranged widely between 0.6% (EPILOG) and 7.8% (EPIC). In general, transfusion rates in clinical trials have been lower than those observed in observational series of patients.

Summary

Major advances in PCI have occurred since this procedure was first introduced. Adjunctive pharmacologic therapy both during and after PCI is a key factor in the continued success of PCI. As we continue to advance our knowledge in this area and offer PCI to more and more patients, we must address the dilemma of how to construct more potent combinations of anticoagulant and antiplatelet agents, affording greater protection against ischemic complications, without increasing the risk of bleeding.

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Issues in Pharmacotherapy Practice

The Role of the Pharmacist in Falls Prevention in the Elderly

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Abstract

Background: Falls are a significant health care problem, resulting in significant morbidity and mortality in the elderly population. Previous research has shown that medications play a contributing role in falls. It has also been shown that multifactorial interventions can reduce the risk of falls in community dwelling or institutionalized patients. Even though there are a significant number of publications on falls and falls prevention in the elderly, there is very little published information on the role of the pharmacist in falls prevention. The objective of this paper is to review the literature on falls intervention to determine the role of the pharmacist in falls intervention programs.

Methods: The published literature was reviewed by searching CINAHL (1996-2001), Medline (1966-2001), EMBASE (1998-2001), Best Evidence (1991-2001), and Nursing Collection (1995-2001). All databases were searched to February 2001. Search terms included “fall(s), elderly, accident, aged, (falls) prevention”. A total of 10 intervention studies were identified, and recommendations from review articles, position papers, and editorials are also included in the review.

Results: The incidence and risks of falls can be decreased most significantly through multifactorial interventions that also include medication review with appropriate modifications to the medication regimen. Education of the patient and health care team is also beneficial in reducing falls. The role of the pharmacist appears to be focused on medication review and education.

Conclusion: Pharmacists can play a potentially important role in reducing the risks of

falls in the elderly.

J Inform Pharmacother 2001;6:314-324.

Introduction

Falls are the most frequent accident involving the elderly and are associated with a high mortality rate. (1,2) There is a perception, even among seniors, that falling is a natural part of aging but this is incorrect. (1,3) Falls may be due to a combination of underlying medical illnesses, medications, environmental hazards and social factors. (1,4-6)

Improvements in the underlying disease states may occur if problems are diagnosed and treated early. (6) Unfortunately, it is rare that preventive measures are implemented because the cause of falls is not usually investigated. (7) Even if the underlying condition cannot be managed, a number of interventions can lower the risk of falling. (6)

The prevalence of falls in the community dwelling elderly is 25-50% and appears to increase with age. (1,8) The annual incidence of falls in long-term care facilities (LTCF) has been found to be 1600 per 1000 patients, or at least three-fold the rate of falls in the community. (9,10) The impact of falls on the elderly population is substantial. Besides the financial cost of acute management, rehabilitation and long-term care placement, there is significant cost in terms of morbidity and mortality, including soft tissue injury, fractures (hip, wrist) and complications of immobility such as respiratory infections and thrombotic events. (1,11-14) Following a hip fracture a patient may never recover his/her previous level of function which in turn increases the risk of institutionalization. (15-18) Mortality following falls is also a significant concern. While only 14% of all falls occur in the elderly, this age group accounts for greater than 50% of all fall-related deaths. (19) Falls can also cripple patients emotionally, making them afraid to leave their homes or do activities that they perceive as increasing their risk of falling. (1,13) For these reasons, falls have been identified as a high priority area for professional intervention. (20,21)

Many studies designed to test interventions to reduce falls have included a component of medication intervention (e.g. reducing doses, discontinuing medications), or education of patients or health care providers about high-risk medications. There have been numerous observational studies that have linked specific medication classes with falls in the elderly. Sobel et al. found that approximately one-fifth of falls were non-environmental (i.e. most likely due to a medical or medication related problem) and therefore would be of great interest to the pharmacist. (22)

The type of medication administered (e.g. psychotropics or antiarrhythmics) and the number of medications used has been associated with falls. (23-38) Many of the disease states or conditions that community pharmacists frequently encounter have also been identified as risk factors. (8,13,35,39-51) Thus, it appears that there is ample opportunity for pharmacists to play a significant role in falls prevention.

Pharmacists have recently been shown to make substantial benefits by intervening in areas such as CHF management and critical care. (52-55) Blakey and Hixson-Wallace recently reported that pharmacists can reduce costs and provide clinical benefit by decreasing ADRs and reducing the number of medications in an ambulatory geriatric clinic. (56) Gurwitz et al. have also found that pharmacists can decrease costs and the number of medications used per patient in nursing homes. (57)

The purpose of this paper is to review and summarize falls intervention studies and falls literature that may involve a pharmacist or involve interventions that could be implemented by a pharmacist.

Methods

This study involved a qualitative systematic review of the published literature. The literature was reviewed by searching CINAHL (1996-2001), Medline (1966-2001), EMBASE (1988-2001), Best Evidence (1991-2001), and Nursing Collection (1995-2001). All databases were searched to February 2001. Search terms included "fall(s), elderly, accident, aged, (falls) prevention". The search was limited to articles published in English.

Studies that included a medication or educational intervention to reduce falls in the elderly (either in the community, institution, or LTCF) were included. Publications, including review articles, editorials, position papers, letters to the editor, and studies that did not focus on educational or medication interventions were reviewed for recommendations and suggestions for potential interventions that would be applicable to pharmacy practice.

All articles were reviewed and categorized by the author. Two broad categories were used: "interventions" and "recommendations". Information about the interventions that have been studied to reduce the incidence of falls, evidence supporting the use of these interventions, and what types of interventions a pharmacist can do to assist in the reduction of falls are presented here.

Results

For the published interventions, twelve studies were excluded because their focus was on community interventions that did not include education or medication adjustments, three studies were excluded because the focus was only on exercise, and two pilot studies were excluded because complete results were not included. Articles included were 6 randomized controlled trials, 3 cohort studies, 1 case series, and 3 reviews of institutional falls prevention protocols. For the recommendations category, all articles dealing with falls prevention that were not included in the “interventions” category were included. Twenty-seven review articles, 3 position papers, and 8 cohort studies, and 4 case control studies were reviewed and included.

Multi-Faceted Interventions

While many health care disciplines and various interventions play a role in this multifactorial problem, Burtcher has noted that medication adjustment and exercise are probably the most important interventions, but he did recognize that it is difficult to identify which single intervention plays the most important role. (58) Tinetti et al. emphasized that multifactorial problems will require a multi-factorial intervention to decrease the problem. (59,60) While it may seem appropriate to study each intervention individually, it is evident from previous research that intervening on one specific factor does not significantly reduce falls in the elderly. (54) The information presented below focuses specifically on medication-related interventions, but the reader should keep in mind that these interventions are meant to be part of the interdisciplinary and multifactorial management of falls in the elderly.

Intervention Studies

A landmark randomized, controlled trial used a multi-factorial intervention to reduce falls in community dwelling seniors at least 70 years of age with at least one risk factor for falls. (61) One component of the intervention was adjusting the use of high-risk medications such as sedatives and reducing the total number of medications received, in combination with behavioural instructions, exercise programs, and social visits. At the one-year follow-up, there was a significant reduction in falls in the intervention group (35% vs. 47%, $p=0.04$). The interventions were also successful at reducing polypharmacy (defined as taking at least 4 prescription medications, 63% vs. 86%, $p=0.009$), but it was not effective in reducing specific sedative use. As a result of the intervention, physicians

reported having a heightened awareness of the relationship between medications and falls.

Another recent randomized controlled trial involved an evaluation of a tapering dose program that designed to reduce the dosage of psychotropic medications administered by reformulating the products in smaller doses. (62) In this study, pharmacists compounded the medications to make dose tapering more manageable for patients. The authors reported that this intervention resulted in a decline in the incidence of falls in the LTCF setting for the intervention group when compared to the control group with 1.16 falls/person/year and 0.52 falls/person/year, respectively (95% CI -0.07, -1.35).

Unfortunately, for those patients receiving psychotropic drugs for insomnia, quality of sleep deteriorated when the medications were withdrawn. The authors felt that additional educational intervention and use of non-pharmacological methods to manage the insomnia may have benefited these distressed patients.

Gray et al. have published a case-series of their falls assessment clinic. In their report, these authors have described a Falls Evaluation Clinic in which patients age ≥ 60 years were eligible for referral for multidisciplinary assessment and interventions to reduce falls risk. (63) The pharmacists focused on psychotropic medications, and their suggestions resulted in discontinuation/adjustment of medications in 73.3% of recommendations over a 2-year period. The team found that education of the patients and the prescribers was necessary in order to reduce psychotropic drug use. While the authors did not report a reduction in falls over the study period, this report does indicate that pharmacists can improve the medication profiles of patients, by making recommendations to minimize high-risk medications that may potentially contribute to falls.

In 1988, Wolf-Klein et al. reported the results of a comprehensive multidisciplinary Falls Clinic. Unfortunately, a pharmacist was not included in the staff of this clinic. (64) In this 36-patient cohort study only the geriatrician reviewed medications, identified drug interactions (8/36 patients) and made suggestions regarding medication dosage adjustments. The study found that 77% of patients experienced no further falls at one year. The authors concluded that a multidisciplinary team approach is necessary for successful management of falls prevention.

In 1992, Tideiksaar reported the results of a one-year multi-faceted community based project involving three major interventions: (i) health care professional education; (ii) identification of patients who had fallen or were at risk of falling; and (iii) community services developed to modify patient's homes to decrease risk. (65) The education

component of the intervention was directed at physicians and community nurses, and focused on the causes, evaluation, and management of falls. Nurses and physicians were encouraged to ask patients about falls during routine examinations. Patients who suffered from uncontrolled medical problems or cited environmental hazards at admission were followed for two years. At two years, 75% of these patients had not experienced falls. The authors noted that once the medical problems (e.g. hypertension, parkinsonism and others) were addressed, the incidence of falls decreased. In addition, the physicians and nurses reported that their greater knowledge about falls helped them identify potential hazards. However, the study was not designed to assess directly health care worker's knowledge and the potential relationship with the actual incidence of falls themselves.

In 1994, Wagner and colleagues reported the results of their randomized, controlled trial that targeted patients who used prescription medications that could increase the risk of falls or mental, hearing, or visual impairment. (66) A random sample of ambulatory seniors (age ≥ 65 years) was selected from a health maintenance organization enrollment database (n= 1559). The patients were randomly assigned to one of three groups: (i) experimental intervention (a nurse assessment with specific targeted interventions, including a focus on prescription medications with subsequent referral to another health care professional if necessary; (ii) nurse visit only (chronic disease states were counseled on, but follow-up activities were limited); and (iii) a standard care control group. In the experimental intervention group, the nurse screened the patients and forwarded information to the pharmacist, who subsequently reviewed the medical record for psychoactive drugs, cardiovascular agents, or any medications that could cause drowsiness or dizziness. Written recommendations were forwarded by the pharmacist to the primary care team. While 78% of patients received a pharmacist medication review, the investigators reported that there was no change in mortality, falls, prescription drug use, or functional outcomes (e.g. days of restricted activity) at the end of the 2-year study period. However, a significant limitation of the trial was that active interventions were included only in the first year without repeat interventions or recommendations. Accordingly, it may be concluded from this trial that "modest" medication review intervention are not effective over a two year period when these interventions involve a single recommendation episode. The authors suggest that interventions must be done repetitively and with more extensive monitoring to be effective. While more involved and long-term intervention by the health care team may improve falls prevention, such intervention is much more costly and labour intensive than a one time intervention.

Two additional randomized, controlled trials have been published that involved an assessment of the effect of discontinuing psychotropic medications on the reduction in

falls in LTCF setting. (67,68) In one study (67), Ray et al used a multi-disciplinary Falls Consultation Service (including a geropsychiatric nurse, a psychiatrist, but no pharmacist), while the other (68) employed a nurse practitioner to undertake assessments after being trained by the physician investigators. The information collected by the nurse was presented to the physicians on the research team who subsequently prepared a set of recommendations for each patient and forwarded this information to the patient's primary care physician. (68) The recommendations included evaluation for rehabilitation therapies, further diagnostic evaluation, management of chronic disease states (e.g. congestive heart failure), medication changes, and environmental modifications. The investigators found that all interventions, including environmental modifications and psychotropic drug use reduction, resulted in a 19% (54.1% vs. 43.8%, $p=0.03$) reduction in falls. In the second study, Rubenstein et al. did not find a reduction in falls or death, but did report 26% fewer hospitalizations ($p<0.05$). (68)

A study by Avorn et al, including 6 matched pairs of LTCF randomly assigned to education intervention of the health care providers, was designed to reduce psychoactive medications. (69) One LTCF from each pair was assigned the intervention, while the other matched LTCF was used as the control. The interventions included extensive education to emphasize alternatives to sedation for behavioural problems or insomnia, and to make the staff aware of adverse drug reactions. Both pharmacists and physicians taught in the educational program. The educational sessions were given to physicians and nursing staff. The reduction in psychoactive drug use was monitored using a psychoactive drug use score the authors developed before the study began. The intervention was successful in reducing the use of psychoactive medications or switching them to safe alternatives (decrease in drug use score, 27% vs. 8%, $p=0.02$), but more patients had difficulty sleeping ($p=ns$) and patients reported more depressive symptomatology (56% vs. 27%, 95% CI 1.1-3.9). The study was not designed to look at a decrease in falls or other traumatic injuries.

A number of letters were written criticizing this study because there was an across-the-board reduction in psychoactive medications, when some patients likely would have benefited from staying on the medication. (70-72) Nygaard pointed out that patients with anxiety or depressive states can fall and psychotropic medications may actually benefit these patients. (73) Certainly such medications should not be empirically withdrawn, but each patient evaluated individually. While the objections are valid, the study did show that an educational intervention involving a pharmacist can be effective at altering the pattern of medication use in a LTCF. Pharmacists must use their best clinical and professional judgment for each patient, and simply making a recommendation for the

purpose of suggesting a medication change would be inappropriate. To simply try to decrease medication use, without considering the risks of that change on the patient, would be inappropriate and may lead to other consequences (such as untreated symptoms or complaints) that would decrease the patient's quality of life. The results of this study can be interpreted such that pharmacist intervention can result in significant changes in medication use, but it is still important that the pharmacist make those recommendations with the best interest of the patient in mind. (69)

The studies discussed above indicate that interventions to reduce falls are most successful when they are multidisciplinary, multifactorial, include medication regimen improvements, and have repeated intervention with the patient. While not all these studies included pharmacists on the intervention team, medication changes played an important role in the multifactorial management.

Are Patients Willing to Accept Interventions

In a 1994 study involving geriatric community patients, Hornbrook et al. found that most patients were willing to attend education sessions, have home visits, or even have one-on-one sessions with instructors to learn about ways of reducing falls. (74) Individuals were also willing to accept changes in their medication regimen, even more so than changes to their environment or diet. (75) Thompson also found that almost all (90%) of geriatric community study participants were willing to have their homes modified after inspection in an effort to reduce the likelihood of falls. (76) In contrast, Wagner et al. noted that only a minority of patients were willing to make environmental changes, but 78% were willing to undergo a medication review. (66) However, further research is required to determine if agreement of a medication review is indicative of acceptance and implementation of recommendations for medication change. Schoenfelder et al. found that most patients could be made aware of falls through an educational program, but few were interested in actually making environmental modifications or doing the exercises. (77) It is evident that patients who are at risk are willing to have interventions suggested, but there may be a reluctance to implement or maintain the suggested changes.

Recommendations

While pharmacists appear to have not played a large role in the published falls research, the clinical interventions that can be provided by this health care professional is important for elderly patients at risk of falls. As discussed above, medication

modifications (as part of a multifactorial intervention) can significantly decrease the incidence of falls. The pharmacist should play a pivotal role in medication review, patient and coworker education and patient referral. Some published recommendations are discussed below.

Medication Review

Medication assessment is a necessary component of falls intervention, and should be done to optimize the medication regimen by reducing the potential for adverse drug effects and minimizing the number of high risk medications (most specifically psychotropics). (6,12,22,35,78-82) If a patient has fallen, it is important to obtain a comprehensive medication history in order to determine if the types of medications or the times of administration had an impact on the fall. (1,9)

Kerman et al. has suggested monitoring blood levels of high-risk medications, such as hypnotics, anxiolytics, or cardiac medications in order to monitor for toxic levels. (83) The benefits and costs of such an intervention or the effectiveness of monitoring routine blood levels has not been documented, and is not common practice for falls prevention.

Authors focusing on psychoactive medications recommend discontinuing or lowering the dose, using caution with psychotropics, or using non-pharmacologic alternatives. (33,84-89) Considering that 33% of falls in LTCF and 13% of falls in the community may be attributed in part to psychotropics, it is important to focus on this category of drugs. (84) Other suggestions include using walking aids while using such medications, and a controversial suggestion to attempt drug holidays with careful tapering. While there is minimal evidence to suggest an overall improvement in patient health and quality of life with drug holidays, it is appropriate to re-evaluate medications that may no longer be necessary, and to make appropriate suggestions to taper and discontinue such medications. Lord et al. suggested that antidepressants not be used for nighttime sedation, or any indication other than depression. (90)

One review has looked at studies that optimized medications in nursing homes. (57) The outcomes focused on reducing the number of medications, rather than an outcome such as reducing falls, fractures, or other injuries. Consultant pharmacists are able to reduce the number of medications LTCF residents take, but it has not been shown that this alone will reduce falls. (57,81) Many studies have found polypharmacy to be a risk factor for falls, so it is current practice of consultant pharmacists to review medications in LTCF in order to reduce the number of medications.

Treatment of co-morbid illness, which may be ignored in patients who suffer with dementia, should be a priority for pharmacists working with seniors. Recommendations also include discontinuing medications that can cause cognitive impairment. (91,92)

In summary, a medication review is an important part of reducing falls risk in the elderly. While a complete medication history is important, the most important class of medications to monitor are the psychotropics. Medications should be periodically re-evaluated and a tapering regimen suggested if the medication is no longer necessary. Drug levels should not be ordered for the purpose of falls prevention, but all relevant laboratory parameters, including drug levels, should be monitored, when available, for signs of toxicity or irregularity that may precipitate a fall.

Education

Education, as part of a multifactorial intervention, is necessary in order to reduce the risk of falls. (85,87) Studies discussed above included education of patients (usually done by a nurse), or education of other health care professionals to be aware of falling risks and how to manage patients who fall.

Stevens and Olson recommend providing falls prevention information at “central locations”, which could include community pharmacies or ambulatory clinics. (93) Hindmarsh et al. recommended counseling older patients about the appropriate use of drugs so that they use them correctly and consistently, specifically mentioning pharmacist counseling as improving compliance. (41) Cwikel et al. has noted that education for falls prevention can be given by other seniors (e.g. societies of retired persons). (4) It is also important to educate seniors about the importance of consulting their physician when a fall occurs. For example, a fall may be a sign of a stroke, or may precede subsequent falls. Tinetti et al. has noted that patients are more compliant with interventions regarding falls when they acknowledge the hazard, which can only be done after education. (40)

Education of other health care team members is necessary. The Kellogg Report noted a reduction in hip fractures when the medical and nursing staff of a LTCF were educated about the risks of using sedative-hypnotics, and given alternatives to using such products in the elderly. (1) Gales and Menard published dosing guidelines for benzodiazepines that are used by the drug use evaluation program at their institution. (94) They also distributed pharmacy newsletters focusing on avoidance of long half-life benzodiazepines, administration regimens, and high dosage risks in elderly patients. Prescription alerts

were put into the pharmacy computer system to alert pharmacists about excessive benzodiazepine dosages. These changes were introduced after a retrospective case control study at the institution that found heart failure, digoxin therapy, and administration of 3 or more psychoactive medications were associated with increased patient falls. Further research on the benefit of implementing these changes has not been published.

Various authors have targeted their recommendations at nursing staff. Some of the recommendations include reviewing medications for side effects, reducing CNS depressants, or reducing the number of medications used. (95-99) Other interventions include patient education and counseling about calcium and vitamin D to prevent fractures, and counseling patients about taking new medications. (98,100) Nurses are also encouraged to give inservices and promote education amongst other health care professionals. (100) While these recommendations were directed at the nursing discipline, they would also be very appropriate for pharmacists to consider.

The Canadian Medical Association has published a Medication Use in the Elderly statement in 1993. (101) The authors reported that "...several studies have shown physicians' prescribing knowledge to be inadequate and inappropriate." Certainly pharmacists can be involved in education and support of the interdisciplinary team to optimize medications.

While there is little evidence that education alone reduces the risk of falls, patient education should be considered as a part of a multifactorial intervention can significantly reduce the incidence of falls in elderly patients. Education should include counseling about the risks of medications (e.g. causing dizziness, drowsiness, etc.) and providing information to patients about other non-drug related interventions to reduce their risk of falls. Education of the health care team is also important, and pharmacists should play a role in providing education on the risks and management of medications.

Referral to Other Health Care Professionals

Considering that a comprehensive assessment is necessary, reviewing the home environment, sensory losses, medical problems, alcohol use, and social and psychological factors must involve other disciplines. Duthie has noted no medical cause can be found for 50% of falls. (7) This means that one-half of falls may have an environmental etiology. Pharmacists should be aware that other health care professionals can review the home safety situation, prescribe appropriate exercises to improve balance, strength,

and shorten reaction time. (102,103) Assistance devices (including walking aids, hip protectors, shower bars, etc.) may also be necessary and can be assessed by a physiotherapist or occupational therapist. (104) It is also important for a physiotherapist to explain to a patient how to fall so that if they do fall, they do so in a way that lowers their risk of injury. Patients must also be instructed on how to get up after a fall. Dieticians can also play an important role in improving nutrition and reducing frailty. (75) Social workers should also be involved to set the patient up with appropriate social activities to improve general well-being and lower levels of anxiety and depression. (4)

Sleeper has noted a number of responsibilities of the pharmacist in falls management. One area is referral to a physician and she has listed predictors that would warrant referral. (36) These predictors include muscle weakness, unsteady balance, a fall in the past year, and unnecessary use of multiple or high risk medications.

Conclusion

King and Tinetti have noted that “medication use is potentially the most modifiable risk factor for falls, and, as such, is of particular interest clinically.” (14) While there is not strong evidence for a pharmacist independently intervening to reduce falls, there is significant support for a pharmacist participating on a multidisciplinary team to review medications, provide appropriate suggestions to reduce high risk medications, and provide education to the patient and health care team.

Medications are only part of the larger picture when trying to manage falls. (31) Considering that a number of factors contribute to falls, it is not surprising that an interdisciplinary assessment and intervention would be preferred. (60,93,105) It is important for pharmacists to remember that they play a critical role in reviewing medications, reducing inappropriate medications (by designing appropriate tapering regimens), and monitoring high risk drug use. Education of both patients and other health care providers is also an important role. Pharmacists must also be aware of the skills of other health care professionals in reducing falls and their complications in the elderly. Interventions should always be comprehensive, individualized, creative, and emphasize a team approach. (104)

In conclusion, pharmacists can play a potentially important role in reducing the risks of falls in the elderly.

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The Role of the Pharmacist in Falls Prevention in the Elderly

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Background: Falls are a significant health care problem, resulting in significant morbidity and mortality in the elderly population. Previous research has shown that medications play a contributing role in falls. It has also been shown that multifactorial interventions can reduce the risk of falls in community dwelling or institutionalized patients. Even though there are a significant number of publications on falls and falls prevention in the elderly, there is very little published information on the role of the pharmacist in falls prevention. The objective of this paper is to review the literature on falls intervention to determine the role of the pharmacist in falls intervention programs.

Methods: The published literature was reviewed by searching CINAHL (1996-2001), Medline (1966-2001), EMBASE (1998-2001), Best Evidence (1991-2001), and Nursing Collection (1995-2001). All databases were searched to February 2001. Search terms included "fall(s), elderly, accident, aged, (falls) prevention". A total of 10 intervention studies were identified, and recommendations from review articles, position papers, and editorials are also included in the review.

Results: The incidence and risks of falls can be decreased most significantly through multifactorial interventions that also include medication review with appropriate modifications to the medication regimen. Education of the patient and health care team is also beneficial in reducing falls. The role of the pharmacist appears to be focused on medication review and education.

Conclusions: Pharmacists can play a potentially important role in reducing the risks of falls in the elderly.

J Inform Pharmacother 2001;6:314-324.

Falls are the most frequent accident involving the elderly and are associated with a high mortality rate. (1,2) There is a perception, even among seniors, that falling is a natural part of aging but this is incorrect. (1,3) Falls may be due to a combination of underlying medical illnesses, medications, environmental hazards and social factors. (1, 4-6) Improvements in the underlying disease states may occur if problems are diagnosed and treated early. (6) Unfortunately, it is rare that preventive measures are implemented because the cause of falls is not usually investigated. (7) Even if the underlying condition cannot be managed, a number of interventions can lower the risk of falling. (6)

The prevalence of falls in the community dwelling elderly is 25-50% and appears to increase with age. (1,8) The annual incidence of falls in long-term care facilities (LTCF) has been found to be 1600 per 1000 patients, or at least three-fold the rate of falls in the community. (9,10) The impact of falls on the elderly population is substantial. Besides the financial cost of acute management, rehabilitation and long-term care placement, there is significant cost in terms of morbidity and mortality, including soft tissue injury, fractures (hip, wrist) and complications of immobility such as respiratory infections and thrombotic events. (1,11-14) Following a hip fracture a patient may never recover his/her previous level of function which in turn increases the risk of institutionalization. (15-18) Mortality following falls is also a significant concern. While only 14% of all falls occur in the elderly, this age group accounts for greater than 50% of all fall-related deaths. (19) Falls can also cripple patients emotionally, making them afraid to leave their homes or do activities that they perceive as increasing their risk of falling. (1,13) For these reasons, falls have been identified as a high priority area for professional intervention. (20,21)

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Many studies designed to test interventions to reduce falls have included a component of medication intervention (e.g. reducing doses, discontinuing medications), or education of patients or health care providers about high-risk medications. There have been numerous observational studies that have linked specific medication classes with falls in the elderly. Sobel et al. found that approximately one-fifth of falls were non-environmental (i.e. most likely due to a medical or medication related problem) and therefore would be of great interest to the pharmacist. (22)

The type of medication administered (e.g. psychotropics or antiarrhythmics) and the number of medications used has been associated with falls. (23-38) Many of the disease states or conditions that community pharmacists frequently encounter have also been identified as risk factors. (8,13,35,39-51) Thus, it appears that there is ample opportunity for pharmacists to play a significant role in falls prevention.

Pharmacists have recently been shown to make substantial benefits by intervening in areas such as CHF management and critical care. (52-55) Blakey and Hixson-Wallace recently reported that pharmacists can reduce costs and provide clinical benefit by decreasing ADRs and reducing the number of medications in an ambulatory geriatric clinic. (56) Gurwitz et al. have also found that pharmacists can decrease costs and the number of medications used per patient in nursing homes. (57)

The purpose of this paper is to review and summarize falls intervention studies and falls literature that may involve a pharmacist or involve interventions that could be implemented by a pharmacist.

Methods

This study involved a qualitative systematic review of the published literature. The literature was reviewed by searching CINAHL (1996-2001), Medline (1966-2001), EMBASE (1988-2001), Best Evidence (1991-2001), and Nursing Collection (1995-2001). All databases were searched to February 2001. Search terms included "fall(s), elderly, accident, aged, (falls) prevention". The search was limited to articles published in English.

Studies that included a medication or educational intervention to reduce falls in the elderly (either in the community, institution, or LTCF) were included. Publications, including review articles, editorials, position papers, letters to the editor, and studies that did not focus on educational or medication interventions were reviewed for recommendations and suggestions for potential interventions that would be applicable to pharmacy practice.

All articles were reviewed and categorized by the author. Two broad categories were used: "interventions" and "recommendations". Information about the interventions that have been studied to reduce the incidence of falls, evidence supporting the use of these interventions, and what types of interventions a pharmacist can do to assist in the reduction of falls are presented here.

Results

For the published interventions, twelve studies were excluded because their focus was on community interventions that did not include education or medication adjustments, three studies were excluded because the focus was only on exercise, and two pilot studies were excluded because complete results were not included. Articles included were 6 randomized controlled trials, 3 cohort studies, 1 case series, and 3 reviews of institutional falls prevention protocols. For the recommendations category, all articles dealing with falls prevention that were not included in the "interventions" category were included. Twenty-seven review articles, 3 position papers, and 8 cohort studies, and 4 case control studies were reviewed and included.

Multi-Faceted Interventions

While many health care disciplines and various interventions play a role in this multifactorial problem, Burtscher has noted that medication adjustment and exercise are probably the most important interventions, but he did recognize that it is difficult to identify which single intervention plays the most important role. (58) Tinetti et al. emphasized that multifactorial problems will require a multi-factorial intervention to decrease the problem. (59,60) While it may seem appropriate to study each intervention individually, it is evident from previous

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research that intervening on one specific factor does not significantly reduce falls in the elderly. (54) The information presented below focuses specifically on medication-related interventions, but the reader should keep in mind that these interventions are meant to be part of the interdisciplinary and multifactorial management of falls in the elderly.

Intervention Studies

A landmark randomized, controlled trial used a multi-factorial intervention to reduce falls in community dwelling seniors at least 70 years of age with at least one risk factor for falls. (61) One component of the intervention was adjusting the use of high-risk medications such as sedatives and reducing the total number of medications received, in combination with behavioural instructions, exercise programs, and social visits. At the one-year follow-up, there was a significant reduction in falls in the intervention group (35% vs. 47%, $p=0.04$). The interventions were also successful at reducing polypharmacy (defined as taking at least 4 prescription medications, 63% vs. 86%, $p=0.009$), but it was not effective in reducing specific sedative use. As a result of the intervention, physicians reported having a heightened awareness of the relationship between medications and falls.

Another recent randomized controlled trial involved an evaluation of a tapering dose program that designed to reduce the dosage of psychotropic medications administered by reformulating the products in smaller doses. (62) In this study, pharmacists compounded the medications to make dose tapering more manageable for patients. The authors reported that this intervention resulted in a decline in the incidence of falls in the LTCF setting for the intervention group when compared to the control group with 1.16 falls/person/year and 0.52 falls/person/year, respectively (95% CI -0.07, -1.35). Unfortunately, for those patients receiving psychotropic drugs for insomnia, quality of sleep deteriorated when the medications were withdrawn. The authors felt that additional educational intervention and use of non-pharmacological methods to manage the insomnia may have benefited these distressed patients.

Gray et al. have published a case-series of their falls assessment clinic. In their report, these authors have described a Falls Evaluation Clinic in which patients age ≥ 60 years were eligible for referral for multidisciplinary assessment and interventions to reduce falls risk. (63) The pharmacists focused on psychotropic medications, and their suggestions resulted in discontinuation/adjustment of medications in 73.3% of recommendations over a 2-year period. The team found that education of the patients and the prescribers was necessary in order to reduce psychotropic drug use. While the authors did not report a reduction in falls over the study period, this report does indicate that pharmacists can improve the medication profiles of patients, by making recommendations to minimize high-risk medications that may potentially contribute to falls.

In 1988, Wolf-Klein et al. reported the results of a comprehensive multidisciplinary Falls Clinic. Unfortunately, a pharmacist was not included in the staff of this clinic. (64) In this 36-patient cohort study only the geriatrician reviewed medications, identified drug interactions (8/36 patients) and made suggestions regarding medication dosage adjustments. The study found that 77% of patients experienced no further falls at one year. The authors concluded that a multidisciplinary team approach is necessary for successful management of falls prevention.

In 1992, Tideiksaar reported the results of a one-year multi-faceted community based project involving three major interventions: (i) health care professional education; (ii) identification of patients who had fallen or were at risk of falling; and (iii) community services developed to modify patient's homes to decrease risk. (65) The education component of the intervention was directed at physicians and community nurses, and focused on the causes, evaluation, and management of falls. Nurses and physicians were encouraged to ask patients about falls during routine examinations. Patients who suffered from uncontrolled medical problems or cited environmental hazards at admission were followed for two years. At two years, 75% of these patients had not experienced falls. The authors noted that once the medical problems (e.g. hypertension, parkinsonism and others) were addressed, the incidence of falls decreased. In addition, the physicians and nurses reported that their greater knowledge about falls helped them identify potential

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hazards. However, the study was not designed to assess directly health care worker's knowledge and the potential relationship with the actual incidence of falls themselves.

In 1994, Wagner and colleagues reported the results of their randomized, controlled trial that targeted patients who used prescription medications that could increase the risk of falls or mental, hearing, or visual impairment. (66) A random sample of ambulatory seniors (age ≥ 65 years) was selected from a health maintenance organization enrollment database (n= 1559). The patients were randomly assigned to one of three groups: (i) experimental intervention (a nurse assessment with specific targeted interventions, including a focus on prescription medications with subsequent referral to another health care professional if necessary; (ii) nurse visit only (chronic disease states were counseled on, but follow-up activities were limited); and (iii) a standard care control group. In the experimental intervention group, the nurse screened the patients and forwarded information to the pharmacist, who subsequently reviewed the medical record for psychoactive drugs, cardiovascular agents, or any medications that could cause drowsiness or dizziness. Written recommendations were forwarded by the pharmacist to the primary care team. While 78% of patients received a pharmacist medication review, the investigators reported that there was no change in mortality, falls, prescription drug use, or functional outcomes (e.g. days of restricted activity) at the end of the 2-year study period. However, a significant limitation of the trial was that active interventions were included only in the first year without repeat interventions or recommendations. Accordingly, it may be concluded from this trial that "modest" medication review intervention are not effective over a two year period when these interventions involve a single recommendation episode. The authors suggest that interventions must be done repetitively and with more extensive monitoring to be effective. While more involved and long-term intervention by the health care team may improve falls prevention, such intervention is much more costly and labour intensive than a one time intervention.

Two additional randomized, controlled trials have been published that involved an assessment of the effect of discontinuing psychotropic medications on the reduction in falls in LTCF setting. (67,68) In one

study (67), Ray et al used a multi-disciplinary Falls Consultation Service (including a geropsychiatric nurse, a psychiatrist, but no pharmacist), while the other (68) employed a nurse practitioner to undertake assessments after being trained by the physician investigators. The information collected by the nurse was presented to the physicians on the research team who subsequently prepared a set of recommendations for each patient and forwarded this information to the patient's primary care physician. (68) The recommendations included evaluation for rehabilitation therapies, further diagnostic evaluation, management of chronic disease states (e.g. congestive heart failure), medication changes, and environmental modifications. The investigators found that all interventions, including environmental modifications and psychotropic drug use reduction, resulted in a 19% (54.1% vs. 43.8%, $p=0.03$) reduction in falls. In the second study, Rubenstein et al. did not find a reduction in falls or death, but did report 26% fewer hospitalizations ($p<0.05$). (68)

A study by Avorn et al, including 6 matched pairs of LTCF randomly assigned to education intervention of the health care providers, was designed to reduce psychoactive medications. (69) One LTCF from each pair was assigned the intervention, while the other matched LTCF was used as the control. The interventions included extensive education to emphasize alternatives to sedation for behavioural problems or insomnia, and to make the staff aware of adverse drug reactions. Both pharmacists and physicians taught in the educational program. The educational sessions were given to physicians and nursing staff. The reduction in psychoactive drug use was monitored using a psychoactive drug use score the authors developed before the study began. The intervention was successful in reducing the use of psychoactive medications or switching them to safe alternatives (decrease in drug use score, 27% vs. 8%, $p=0.02$), but more patients had difficulty sleeping ($p=ns$) and patients reported more depressive symptomatology (56% vs. 27%, 95% CI 1.1-3.9). The study was not designed to look at a decrease in falls or other traumatic injuries.

A number of letters were written criticizing this study because there was an across-the-board reduction in psychoactive medications, when some patients likely would have benefited from staying on the medication. (70-72) Nygaard pointed out that

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patients with anxiety or depressive states can fall and psychotropic medications may actually benefit these patients. (73) Certainly such medications should not be empirically withdrawn, but each patient evaluated individually. While the objections are valid, the study did show that an educational intervention involving a pharmacist can be effective at altering the pattern of medication use in a LTCF. Pharmacists must use their best clinical and professional judgment for each patient, and simply making a recommendation for the purpose of suggesting a medication change would be inappropriate. To simply try to decrease medication use, without considering the risks of that change on the patient, would be inappropriate and may lead to other consequences (such as untreated symptoms or complaints) that would decrease the patient's quality of life. The results of this study can be interpreted such that pharmacist intervention can result in significant changes in medication use, but it is still important that the pharmacist make those recommendations with the best interest of the patient in mind. (69)

The studies discussed above indicate that interventions to reduce falls are most successful when they are multidisciplinary, multifactorial, include medication regimen improvements, and have repeated intervention with the patient. While not all these studies included pharmacists on the intervention team, medication changes played an important role in the multifactorial management.

Are People Willing to Accept Interventions

In a 1994 study involving geriatric community patients, Hornbrook et al. found that most patients were willing to attend education sessions, have home visits, or even have one-on-one sessions with instructors to learn about ways of reducing falls. (74) Individuals were also willing to accept changes in their medication regimen, even more so than changes to their environment or diet. (75) Thompson also found that almost all (90%) of geriatric community study participants were willing to have their homes modified after inspection in an effort to reduce the likelihood of falls. (76) In contrast, Wagner et al. noted that only a minority of patients were willing to make environmental changes, but 78% were willing to undergo a medication review. (66) However, further research is required to determine if agreement of a medication review is indicative of acceptance and implementation of recommendations for medication

change. Schoenfelder et al. found that most patients could be made aware of falls through an educational program, but few were interested in actually making environmental modifications or doing the exercises. (77) It is evident that patients who are at risk are willing to have interventions suggested, but there may be a reluctance to implement or maintain the suggested changes.

Recommendations

While pharmacists appear to have not played a large role in the published falls research, the clinical interventions that can be provided by this health care professional is important for elderly patients at risk of falls. As discussed above, medication modifications (as part of a multifactorial intervention) can significantly decrease the incidence of falls. The pharmacist should play a pivotal role in medication review, patient and coworker education and patient referral. Some published recommendations are discussed below.

Medication Review

Medication assessment is a necessary component of falls intervention, and should be done to optimize the medication regimen by reducing the potential for adverse drug effects and minimizing the number of high risk medications (most specifically psychotropics). (6,12,22,35,78-82) If a patient has fallen, it is important to obtain a comprehensive medication history in order to determine if the types of medications or the times of administration had an impact on the fall. (1,9)

Kerman et al. has suggested monitoring blood levels of high-risk medications, such as hypnotics, anxiolytics, or cardiac medications in order to monitor for toxic levels. (83) The benefits and costs of such an intervention or the effectiveness of monitoring routine blood levels has not been documented, and is not common practice for falls prevention.

Authors focusing on psychoactive medications recommend discontinuing or lowering the dose, using caution with psychotropics, or using non-pharmacologic alternatives. (33,84-89) Considering that 33% of falls in LTCF and 13% of falls in the community may be attributed in part to

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psychotropics, it is important to focus on this category of drugs. (84) Other suggestions include using walking aids while using such medications, and a controversial suggestion to attempt drug holidays with careful tapering. While there is minimal evidence to suggest an overall improvement in patient health and quality of life with drug holidays, it is appropriate to re-evaluate medications that may no longer be necessary, and to make appropriate suggestions to taper and discontinue such medications. Lord et al. suggested that antidepressants not be used for nighttime sedation, or any indication other than depression. (90)

One review has looked at studies that optimized medications in nursing homes. (57) The outcomes focused on reducing the number of medications, rather than an outcome such as reducing falls, fractures, or other injuries. Consultant pharmacists are able to reduce the number of medications LTCF residents take, but it has not been shown that this alone will reduce falls. (57,81) Many studies have found polypharmacy to be a risk factor for falls, so it is current practice of consultant pharmacists to review medications in LTCF in order to reduce the number of medications.

Treatment of co-morbid illness, which may be ignored in patients who suffer with dementia, should be a priority for pharmacists working with seniors. Recommendations also include discontinuing medications that can cause cognitive impairment. (91,92)

In summary, a medication review is an important part of reducing falls risk in the elderly. While a complete medication history is important, the most important class of medications to monitor are the psychotropics. Medications should be periodically re-evaluated and a tapering regimen suggested if the medication is no longer necessary. Drug levels should not be ordered for the purpose of falls prevention, but all relevant laboratory parameters, including drug levels, should be monitored, when available, for signs of toxicity or irregularity that may precipitate a fall.

Education

Education, as part of a multifactorial intervention, is necessary in order to reduce the risk of falls.

(85,87) Studies discussed above included education of patients (usually done by a nurse), or education of other health care professionals to be aware of falling risks and how to manage patients who fall.

Stevens and Olson recommend providing falls prevention information at "central locations", which could include community pharmacies or ambulatory clinics. (93) Hindmarsh et al. recommended counseling older patients about the appropriate use of drugs so that they use them correctly and consistently, specifically mentioning pharmacist counseling as improving compliance. (41) Cwikel et al. has noted that education for falls prevention can be given by other seniors (e.g. societies of retired persons). (4) It is also important to educate seniors about the importance of consulting their physician when a fall occurs. For example, a fall may be a sign of a stroke, or may precede subsequent falls. Tinetti et al. has noted that patients are more compliant with interventions regarding falls when they acknowledge the hazard, which can only be done after education. (40)

Education of other health care team members is necessary. The Kellogg Report noted a reduction in hip fractures when the medical and nursing staff of a LTCF were educated about the risks of using sedative-hypnotics, and given alternatives to using such products in the elderly. (1) Gales and Menard published dosing guidelines for benzodiazepines that are used by the drug use evaluation program at their institution. (94) They also distributed pharmacy newsletters focusing on avoidance of long half-life benzodiazepines, administration regimens, and high dosage risks in elderly patients. Prescription alerts were put into the pharmacy computer system to alert pharmacists about excessive benzodiazepine dosages. These changes were introduced after a retrospective case control study at the institution that found heart failure, digoxin therapy, and administration of 3 or more psychoactive medications were associated with increased patient falls. Further research on the benefit of implementing these changes has not been published.

Various authors have targeted their recommendations at nursing staff. Some of the recommendations include reviewing medications for side effects, reducing CNS depressants, or reducing the number of medications used. (95-99) Other

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interventions include patient education and counseling about calcium and vitamin D to prevent fractures, and counseling patients about taking new medications. (98,100) Nurses are also encouraged to give inservices and promote education amongst other health care professionals. (100) While these recommendations were directed at the nursing discipline, they would also be very appropriate for pharmacists to consider.

The Canadian Medical Association has published a Medication Use in the Elderly statement in 1993. (101) The authors reported that "...several studies have shown physicians' prescribing knowledge to be inadequate and inappropriate." Certainly pharmacists can be involved in education and support of the interdisciplinary team to optimize medications.

While there is little evidence that education alone reduces the risk of falls, patient education should be considered as a part of a multifactorial intervention can significantly reduce the incidence of falls in elderly patients. Education should include counseling about the risks of medications (e.g. causing dizziness, drowsiness, etc.) and providing information to patients about other non-drug related interventions to reduce their risk of falls. Education of the health care team is also important, and pharmacists should play a role in providing education on the risks and management of medications.

Referral to other Health Care Professionals

Considering that a comprehensive assessment is necessary, reviewing the home environment, sensory losses, medical problems, alcohol use, and social and psychological factors must involve other disciplines. Duthie has noted no medical cause can be found for 50% of falls. (7) This means that one-half of falls may have an environmental etiology. Pharmacists should be aware that other health care professionals can review the home safety situation, prescribe appropriate exercises to improve balance, strength, and shorten reaction time. (102,103) Assistance devices (including walking aids, hip protectors, shower bars, etc.) may also be necessary and can be assessed by a physiotherapist or occupational therapist. (104) It is also important for a physiotherapist to explain to a patient how to fall so that if they do fall, they do so in a way that lowers

their risk of injury. Patients must also be instructed on how to get up after a fall. Dieticians can also play an important role in improving nutrition and reducing frailty. (75) Social workers should also be involved to set the patient up with appropriate social activities to improve general well-being and lower levels of anxiety and depression. (4)

Sleeper has noted a number of responsibilities of the pharmacist in falls management. One area is referral to a physician and she has listed predictors that would warrant referral. (36) These predictors include muscle weakness, unsteady balance, a fall in the past year, and unnecessary use of multiple or high risk medications.

Conclusion

King and Tinetti have noted that "medication use is potentially the most modifiable risk factor for falls, and, as such, is of particular interest clinically." (14) While there is not strong evidence for a pharmacist independently intervening to reduce falls, there is significant support for a pharmacist participating on a multidisciplinary team to review medications, provide appropriate suggestions to reduce high risk medications, and provide education to the patient and health care team.

Medications are only part of the larger picture when trying to manage falls. (31) Considering that a number of factors contribute to falls, it is not surprising that an interdisciplinary assessment and intervention would be preferred. (60,93,105) It is important for pharmacists to remember that they play a critical role in reviewing medications, reducing inappropriate medications (by designing appropriate tapering regimens), and monitoring high risk drug use. Education of both patients and other health care providers is also an important role. Pharmacists must also be aware of the skills of other health care professionals in reducing falls and their complications in the elderly. Interventions should always be comprehensive, individualized, creative, and emphasize a team approach. (104)

In conclusion, pharmacists can play a potentially important role in reducing the risks of falls in the elderly.

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The Journal of Informed Pharmacotherapy 2001;6:500.

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Name of site:	Integrity in Science
Type of site:	Site concerned with increasing awareness of conflicts of interest in science related to food, health, and the environment.
Authoring organization:	A project of the Center for Science in the Public Interest, a non-profit Washington, DC-based society.
Sponsors:	CSPI is supported by its members, a newsletter, and donation from private citizens and societies.
Of particular interest to:	All health scientists, and to a lesser degree the public.
Completeness Score (1/5)	3.5
Credibility Score (1/5)	4
Usability Score (1/5)	4
Why is it useful? (what will it help me DO?):	Increase your awareness about the pervasiveness of conflicts-of-interest in the everyday scientific process clinicians rely upon for making decisions.
Commentary:	This is an ambitious project which acts mainly as a clearinghouse for information published in the lay press and medical journals concerning conflicts of interest. The conflict-of-interest guidelines compiled from various reputable sources and listed under "Resources" is especially helpful for scientists struggling with these issues. The most ambitious feature of this project is the database of scientists and non-profit organizations' ties to industry. The group is taking declarations made in journals, the lay press, and voluntarily submitted to them and entering them into this searchable database so anyone can look up the name of any scientist. Of course, only a few names are listed under most of the universities I tried, but as this database grows, it could become a powerful (and controversial) tool for scientists and the public to uncover such relationships. What they do that

	information is quite another problem.
URL of site:	http://www.integrityinscience.org
Reviewed by:	Peter Loewen, PharmD

Name of site:	Pharma-Lexicon
Type of site:	Abbreviations database and health directory.
Authoring organization:	Christian Nordqvist and Alastair Hazell
Sponsors:	Supported through banner advertising.
Of particular interest to:	All health care professionals, especially pharmacists.
Completeness Score (1/5)	5
Credibility Score (1/5)	5
Usability Score (1/5)	4.5
Why is it useful? (what will it help me DO?):	Quickly decode acronyms used in all aspects of medicine and pharmacy.
Commentary:	If you thought "ABS" referred to your car's braking system, you might be surprised to learn that it also denotes Autologous Blood Salvage, Australian Bureau of Statistics, American Board of Sexology, American Board of Surgery, American Brachytherapy Society, Animal Behavior Society, and Acrylonitrile butadiene styrene. That's the sort of detail you'll find when trying to decode the many acronyms you encounter during your everyday practice by using this site. The searches are very fast and it identified most of the oddball abbreviations I threw at it. Another unique feature of this site is its directories (complete with web addresses) of the world's health ministries, colleges of pharmacy, and pharmacy/medical associations. I can't think of another way of accessing this sort of information so quickly and easily.
URL of site:	http://www.pharma-lexicon.com/
Reviewed by:	Peter Loewen, Pharm.D.

Name of site:	Evidence Based Medicine Toolkit
Type of site:	Users guide to critical appraisal of clinical research.
Authoring organization:	University of Alberta Faculty of Medicine
Sponsors:	none
Of particular interest to:	Pharmacists and physicians interested in enhancing their literature appraisal skills.

Completeness Score (1/5)	4
Credibility Score (1/5)	5
Usability Score (1/5)	4.5
Why is it useful? (what will it help me DO?):	Develop or improve your literature appraisal skills.
Commentary:	This site is based on the JAMA series of reviews aimed at giving clinicians a framework for evaluating different types of clinical studies. Therefore, although not entirely unique, this site gives users a quick reference to some algorithms which may be useful in critiquing studies. Studies of harm, diagnosis, therapy/prevention and prognosis are covered, as are guidelines, systematic reviews, and economic analysis. A handy table of brief definitions used in the algorithms is well hyperlinked. Although not an exhaustive reference on how to interpret the literature, this site offers a quick refresher on asking the right questions which any clinical can benefit from and any student can use as a framework for critiquing the literature. Astute readers will note that the framework promoted by this site is the same as the JIP's framework for <u>Evidence-Based Reviews of the Pharmacotherapeutic Literature</u>
URL of site:	http://www.med.ualberta.ca/ebm/ebm.htm
Reviewed by:	Peter Loewen, Pharm.D.

Name of site:	EBandolier
Type of site:	An general evidence-based health care site.
Authoring organization:	Bandolier
Sponsors:	Britain's National Health Service, other sponsors including pharmaceutical companies (unrestricted grants)
Of particular interest to:	All pharmacotherapy practitioners.
Completeness Score (1/5)	4
Credibility Score (1/5)	4.5
Usability Score (1/5)	3.5
Why is it useful? (what will it help me DO?):	Provides one-stop shopping for reviews of the published evidence across a broad array of therapeutic issues.

Commentary: EBandolier is the independent electronic version of Bandolier, a respected source of evidence-based information for practitioners in Britain. The site bills itself as providing "'tertiary' publishing, distilling the information from (secondary) reviews of (primary) trials and making it comprehensible".

EBandolier's reviewers provide insightful critiques of the literature in a timely fashion-- usually with a month or two of landmark studies being published. Each month a digest of the latest reviews is published online.

All the content is free. Pharmaceutical industry sponsorship, though declared a part of EBando's funding structure, is not evident and the site is ad-free.

The content is divided into numerous sub-specialties for quicker access to the data you are interested in.

URL of site: <http://www.jr2.ox.ac.uk/bandolier/>

Reviewed by: Peter Loewen, Pharm.D.

Name of site: **The Natural Pharmacist**

Type of site: Database/encyclopedia of natural pharmaceutical products

Authoring organization: TheNaturalPharmacist.com, a division of Prima Publishing, a private book publisher.

Sponsors: Prima Publishing

Of particular interest to: Pharmacists and consumers interesting in natural pharmaceuticals.

Completeness Score (/5) 4.5

Credibility Score (/5) 4

Usability Score (/5) 4.5

Why is it useful? (what will it help me DO?): Provides comprehensive information about natural products.

Commentary: There are numerous online sources for herbal products springing up on the web all the time, some of which are credible and complete. TheNaturalPharmacist is one of the better sources, and best of all, its free.

Each herb's monograph contains all the basics you'd expect, plus "What is the scientific evidence for X" with discussions of clinical studies. Drug interactions are well covered and extensive reference lists were provided for most of the monographs I have reviewed.

When you register as a health professional (free & instant), you gain access to a separate database of monographs which include much more detailed information about each substance (mechanisms, pharmacology, history, research evidence, etc).

I have not seen any banner ads on the site, and I presume it to be funded through sales of the books which are available on the site.

This is definitely a source of herbal information that I will consult frequently because of its easy accessibility.

URL of site: <http://www.tnp.com/>

Reviewed by: [Peter Loewen](#), Pharm.D.

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Journal of Informed Pharmacotherapy 2001;7 (Oct-Dec)

Editorial

- The Only Thing We have to Fear is...Fear Itself
Peter Jewesson



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**Updated
April 15, 2002**

Editorial

The Only Thing We have to Fear is...Fear Itself

These famous words were spoken by Franklin D. Roosevelt (FDR) almost 70 years ago, but they still ring true today.

Following the tragic events of September 11, 2001, we have all been inundated with media coverage of terrorism on North American soil, troops at war in Afghanistan, Anthrax cases and the elevation of fear-based drug marketing to a new height. By now you've probably heard about the recent NBC news report during which Tom Brokaw held up a prescription bottle declared "In Cipro we trust". Once again an equally effective, but older drug (i.e. doxycycline) has been relegated to the back bench. More disconcerting is the fact that sales of ciprofloxacin have apparently tripled due to drug stockpiling. Don't get me started on the issue of generic ciprofloxacin supplies. So much for the quest for antibiotic stewardship. We haven't seen paranoia like this since late 1999. Remember the preparations for Y2K? It looks like we really haven't learned any lessons.

Although overlooked in the flurry of recent events, there is another important battle being fought this fall. Perhaps you managed to break away from these news stories long enough to read the article published in the September 10, 2001 issue of CBC News Online. As identified by the author, some of the world's leading medical journals have signed a pact aimed at ferreting out biased research and are adopting tougher guidelines to stop pharmaceutical companies from interfering in drug research. No small task. Several journals (including the Canadian Medical Association Journal, the New England Journal of Medicine, the Journal of the American Medical Association, The Lancet, the British Medical Journal, Annals of Internal Medicine) now claim that they will refuse to publish (or even review) any papers involving research that relied on data and rights to publish that was controlled by pharmaceutical companies. Should this occur, we can probably expect future issues of these journals to be relatively thin. Not only would there be fewer papers to publish, I suspect that there will also be fewer advertisements to navigate around.

Most of the clinical drug trials that I have seen conducted in our institution are multi-centre in nature and a quick review of the protocols reveals that, in many cases, the data generated is considered to be the property of the sponsoring company. Just ask Dr. Nancy Olivieri about this situation. By the way, congratulations to Dr. Olivieri are in order for her Civil Justice Foundation award for exposing the dangers of deferiprone.

Let's remember a few realities:

1. Industry is a major sponsor of drug research and publication.

Pharmaceutical companies spend over US\$40 billion annually on research and development. (1) Let's face it, industry involvement in research will exist as long as there is profit in pharmaceuticals. For the sake of health care advancement, let's hope that the spirit of capitalism always accompanies drug development. The pace of progress would slow dramatically without it. At the same time, we need to avoid potential conflict of interest while "dancing with the porcupine". (2) Glassman et al (3) recently described the outcome of a study in which these investigators randomly sampled six professional medical society journals to determine if revenue generated from pharmaceutical advertisement creates potential financial conflicts of interest. The authors reported that estimated advertising revenue for these journals ranged from \$715,000 - \$18,630,000. More importantly, 4 of the 6 nonprofit physician organizations raised as much or more from pharmaceutical advertising as they did from memberships. They concluded that potential financial conflicts of interest may be substantial, although the impact on professional societies' financial independence and behaviour is still unknown.

2. Not all research conducted is published.

As Bardsley demonstrated in his 1998 review of 274 clinical trials, selective reporting of trials with positive outcomes should be expected. (4) Ioannidis revealed in his report of the same year, clinical trials with positive results are submitted and published more rapidly after study completion than negative trials. (5)

3. Not all peer-reviews are created equal.

As Link identified in her 1998 retrospective analysis of two years of original submissions received by the journal Gastroenterology, reviewer bias is a real possibility. (6) This investigator found that while US and non-US reviewers evaluate non-US papers similarly, they tend to evaluate papers submitted by US authors more favourably. In particular, US reviewers appear to have a significant preference for US papers. Potential bias exists in many forms. (7) Be wary.

4. Not all published research is good research.

There are too many examples of this to cite.

5. Not all data collected is presented.

Information that is missing is often as important as the facts that the investigators and publishers have selected to provide. This is a particular problem with the reporting of adverse drug events. (8)

Bottom line, don't believe everything you read. As Lewis et al (2) point out in their recent

commentary regarding university-industry relationships, the duty of universities (and I would extrapolate this to include all health care researchers) is to seek the truth, while the duty of pharmaceutical companies is to generate revenue for their shareholders. Keep this in mind and you'll be able to safely navigate the minefields of the published literature.

The Editors join the nation and the rest of the world in offering condolences to those affected by the attacks in the US. Our thoughts and prayers are also with the allied forces who have joined the action against terrorism. And let's all remember FDR's words as we lead our private, and our professional lives.

Peter J. Jewesson, PhD

J Inform Pharmacother 2001;7:1.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;7:200-203.

Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Extend the treatment, extend the benefit?

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Reviewers_Specialty: Pharmacy/Cardiology/Anticoagulation

Original Citation

Agnelli G, Prandoni P, Santamaria MG, Bagatella P, Iorio A, Bazzan M, Guazzaloca G, Bertoldi A, Tomasi A, Scannapieco G, Ageno W. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med. 2001 Jul 19;345(3):165-9. [PubMed Citation](#)

Overall Study Question

This open-label, multicenter trial was conducted to determine the clinical benefit of extending the three-month course of oral anticoagulant therapy for a first episode of idiopathic proximal deep vein thrombosis (DVT) to a treatment duration of one year. Patients between the ages of 18 and 85 were consecutively enrolled into the study after a first episode of symptomatic, idiopathic proximal DVT. After completing three months of uninterrupted therapy with warfarin or acenocoumarol (target INR 2.0-3.0), eligible patients were randomized to either discontinue oral anticoagulant therapy, or to continue it for an additional nine months. The primary outcome for this study was the symptomatic, objectively confirmed recurrence of venous thromboembolism during a minimum of two years of follow-up.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Patients were randomized after three uninterrupted months of oral anticoagulant therapy without having a recurrence of thromboembolism or bleeding episode.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. Two years of follow-up data for all 267 patients enrolled in the study was available. In addition, the primary analysis was performed on an intention-to-treat basis.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

No. This was an open-label trial. However, an independent, blinded adjudication committee reviewed all suspected outcome events (recurrent thromboembolism and bleeding episodes) and all deaths on the basis of predetermined objective criteria.

4. Were the groups similar at the start of the trial?

Unknown. The authors stated that the groups were similar at baseline, however they only provided summary information regarding sex, age and incidence of initial treatment use of low-molecular weight heparin by group. Although randomized, this was a small trial and some unspecified characteristics could be unbalanced between groups. Unspecified characteristics of interest include the incidence of DVT only at presentation, the number of patients with suspected or confirmed pulmonary embolism at presentation, and the frequency of patients with a family history of venous thromboembolism.

5. Aside from the experimental intervention, were the groups treated equally?

No. All patients were instructed to return for follow-up at 3, 6, and 12 months after randomization and every 6 months thereafter until study completion. Those patients assigned to 12 months of oral anticoagulant therapy were monitored in anticoagulant clinics associated with the study centers for an additional nine months of treatment. The frequency of monitoring was unspecified during this period. Those patients assigned to discontinue treatment after 3 months did not have this additional contact with study personnel. However, it is unlikely that bias was introduced as a result of this additional follow-up since the majority of episodes of recurrent venous thromboembolism (RVTE) were discovered after treatment was discontinued.

What were the Results?

1. How large was the treatment effect?

Recruitment was terminated prematurely when the results of a planned interim analysis indicated the treatment effect did not meet the a priori criterion for effectiveness. The intention-to-treat analysis revealed that 21 of the 134 patients assigned to 12 months of therapy experienced an episode of RVTE (15.7%, average follow-up, 37.8 months), as did 21 of the 133 patients who were assigned to the short course therapy treatment arm

(15.8%, average follow-up, 37.2 months). The calculated relative risk was 0.99 (95% confidence interval (CI), 0.57 to 1.73). Per-protocol analysis yielded similar results: 18 of 115 (15.7%) patients assigned to 12 months of therapy, and 21 of 126 (16.7%) assigned to 3 months of therapy experienced RVTE (relative risk 0.94 (95% CI 0.54 to 1.67)). The average time from randomization to RVTE was 11.2 months for those patients assigned to the 3-month treatment arm and 16.0 months in those assigned to 12-month treatment arm.

Major bleeding was defined as: clinically overt and associated with either a decrease in the hemoglobin level of at least 2g/dL or the need for transfusion of ≥ 2 units of red cells, if the bleeding episode was retroperitoneal or intracranial in nature, or if the episode warranted permanent discontinuation of the study drug. Four patients (3.0%) assigned to 12-month therapy experienced nonfatal episodes of major bleeding during oral anticoagulant therapy. None of these patients had an INR above 3.0 at the time of bleeding. Two patients (1.5%) assigned to 3-month therapy suffered fatal bleeding. One episode was an intracranial hemorrhage one month after discontinuation of oral anticoagulation, and the other was a gastrointestinal bleed that occurred 12 months after discontinuation.

2. How precise was the estimate of the treatment effect?

The confidence intervals are quite wide (95% CI 0.57 to 1.73 for the intention-to-treat analysis). This is probably reflective of the relatively small sample size. There does not appear to be a significant skew in the CI that would suggest a possible benefit in the treatment group.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

The results of this study may be generalized to the majority of patients with a first episode of symptomatic idiopathic proximal DVT. The inclusion and exclusion criteria were not exceedingly restrictive. At the time of randomization, 290 consecutive patients met the inclusion criteria, and only 23 were excluded (including 6 who declined to consent), accounting for fewer than 10% of the total number of patients screened. As discussed previously, limited data describing the characteristics of the trial population were available. The average age of patients enrolled in this study (approximately 67 $\pm$ 7 years) appeared older than the average age of patients enrolled in another recent trial of anticoagulation in idiopathic venous thromboembolism (approximately 59 $\pm$ 16 years). (1) The percentage of males in both trials was similar.

2. Were all clinically important outcomes considered?

Yes. Recurrent deep venous thromboembolism, major bleeding, and death were assessed. The location of the recurrent DVT events was not specified in the article. Venous thrombosis of the proximal veins of the legs carries a higher risk of developing

pulmonary embolism than thrombosis of the distal veins. (2) Personal communication with the authors reveals that all 16 RVTE that occurred in those patients receiving 12 months of treatment were proximal in nature. In the 3 month treatment group, 16 of 18 (89%) RVTE were proximal, including popliteal vein location while the remaining events were distally located. (3) Exclusion of the two distal RVTE makes it even less likely that a potential treatment effect was missed.

3. Are the likely treatment benefits worth the potential harms and costs?

Unable to determine. For the first 12 months of the study, the treatment group experienced a reduction in the rate of RVTE. This was at the expense of twice the rate of major bleeding. During the follow-up period after discontinuation of extended anticoagulation, rates of RVTE were in fact higher in the group assigned to continue therapy. Considering that the patients assigned to the treatment group did not derive any sustained benefit, extending the duration of anticoagulation from three months to one year for a first episode of symptomatic idiopathic proximal DVT may not be worth the potential harms and costs for all patients. It appears that RVTE events were simply delayed with continued oral anticoagulant therapy, rather than reduced. In order to recommend continued therapy, the bleeding risks and risk of RVTE in individual patients must be considered.

The rates of major bleeding documented with anticoagulation therapy for RVTE in previous trials is 2-4%, while in the current trial the rate was 3%. (4) Of note, none of the patients who experienced major bleeding events in this trial had INR values in excess of the therapeutic range. It is possible that even enhanced INR monitoring during long-term therapy may not prevent adverse bleeding events. It is this risk of major bleeding during long-term therapy that must be weighed against the consequences of RVTE.

Commentary

The optimal duration of therapy with oral anticoagulants for patients with idiopathic venous thromboembolism has yet to be determined. Results from earlier studies have identified that this population is at increased risk of recurrent thromboembolism. (5,6) The Sixth ACCP Consensus Conference on Antithrombotic Therapy recommends that "patients with a first episode of idiopathic RVTE should be treated for at least 6 months" (7), but it is not clear whether a longer duration of treatment would be advantageous for this high risk group.

Recently, Kearon et al (1) compared an additional 24 months of warfarin therapy with placebo in patients with a first episode of idiopathic thromboembolism who had completed 3 months of initial anticoagulation. They demonstrated a 95 % reduction in the risk of recurrent thromboembolism in patients assigned to extended treatment with warfarin, but did not address whether this advantage would be maintained upon discontinuation of therapy. The current trial was designed to determine if the benefits of extended anticoagulation persists after therapy is discontinued. This trial supports the findings of Kearon et al (1) in that RVTE rates were reduced while patients received continued anticoagulation therapy. However, the results were not maintained after discontinuation, suggesting that prolonging the course of anticoagulation simply delays recurrence until treatment is discontinued. The focus of future trials may need to shift from the determination of an optimal duration of therapy for all patients to the identification of those patients at increased risk of RVTE who would benefit from

indefinite anticoagulation. Patients at highest risk of recurrence must be identified due to the risks, costs and inconvenience associated with long-term anticoagulation therapy.

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Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

The results of this study may be generalized to the majority of patients with a first episode of symptomatic idiopathic proximal DVT. The inclusion and exclusion criteria were not exceedingly restrictive. At the time of randomization, 290 consecutive patients met the inclusion criteria, and only 23 were excluded (including 6 who declined to consent), accounting for fewer than 10% of the total number of patients screened. As discussed previously, limited data describing the characteristics of the trial population were available. The average age of patients enrolled in this study (approximately 67 $\pm$ 7 years) appeared older than the average age of patients enrolled in another recent trial of anticoagulation in idiopathic venous thromboembolism (approximately 59 $\pm$ 16 years). (1) The percentage of males in both trials was similar.

2. Were all clinically important outcomes considered?

Yes. Recurrent deep venous thromboembolism, major bleeding, and death were assessed. The location of the recurrent DVT events was not specified in the article. Venous thrombosis of the proximal veins of the legs carries a higher risk of developing pulmonary embolism than thrombosis of the distal veins. (2) Personal communication with the authors reveals that all 16 RVTE that occurred in those patients receiving 12 months of treatment were proximal in nature. In the 3 month treatment group, 16 of 18 (89%) RVTE were proximal, including popliteal vein location while the remaining events were distally located. (3) Exclusion of the two distal RVTE makes it even less likely that a potential treatment effect was missed.

3. Are the likely treatment benefits worth the potential harms and costs?

Unable to determine. For the first 12 months of the study, the treatment group experienced a reduction in the rate of RVTE. This was at the expense of twice the rate of major bleeding. During the follow-up period after discontinuation of extended anticoagulation, rates of RVTE were in fact higher in the group assigned to continue therapy. Considering that the patients assigned to the treatment group did not derive any sustained benefit, extending the duration of anticoagulation from three months to one year for a first episode of symptomatic idiopathic proximal DVT may not be worth the potential harms and costs for all patients. It appears that RVTE events were simply delayed with continued oral anticoagulant therapy, rather than reduced. In order to recommend continued therapy, the bleeding risks and risk of RVTE in individual patients must be considered.

The rates of major bleeding documented with anticoagulation therapy for RVTE in previous trials is 2-4%, while in the current trial the rate was 3%. (4) Of note, none of the patients who experienced major bleeding events in this trial had INR values in excess of the therapeutic range. It is possible that even enhanced INR monitoring during long-term therapy may not prevent adverse bleeding events. It is this risk of major bleeding during long-term therapy that must be weighed against the consequences of RVTE.

Commentary

The optimal duration of therapy with oral anticoagulants for patients with idiopathic venous thromboembolism has yet to be determined. Results from earlier studies have identified that this population is at increased risk of recurrent thromboembolism. (5,6) The Sixth ACCP Consensus Conference on Antithrombotic Therapy recommends that "patients with a first episode of idiopathic RVTE should be treated for at least 6 months" (7), but it is not clear whether a longer duration of treatment would be advantageous for this high risk group.

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Recently, Kearon et al (1) compared an additional 24 months of warfarin therapy with placebo in patients with a first episode of idiopathic thromboembolism who had completed 3 months of initial anticoagulation. They demonstrated a 95 % reduction in the risk of recurrent thromboembolism in patients assigned to extended treatment with warfarin, but did not address whether this advantage would be maintained upon discontinuation of therapy. The current trial was designed to determine if the benefits of extended anticoagulation persists after therapy is discontinued. This trial supports the findings of Kearon et al (1) in that RVTE rates were reduced while patients received continued anticoagulation therapy. However, the results were not maintained after discontinuation, suggesting that prolonging the course of anticoagulation simply delays recurrence until treatment is discontinued. The focus of future trials may need to shift from the determination of an optimal duration of therapy for all patients to the identification of those patients at increased risk of RVTE who would benefit from indefinite anticoagulation. Patients at highest risk of recurrence must be identified due to the risks, costs and inconvenience associated with long-term anticoagulation therapy acceptable time frame outlined in the AHA Guidelines.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;7:204-207.

Effects of Atorvastatin on Early Recurrent Ischemic Events in Acute Coronary Syndromes. Can We Expect a MIRACL from Cholesterol Lowering Therapy?

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Reviewer's profession/specialty: Interventional Cardiology, Cardiology/Cardiac Transplantation/Risk Reduction

Original Citation

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Overall Study Question

The MIRACL Study was a prospective, randomized, placebo controlled trial conducted in 122 centres. This study was designed to determine whether early initiation of atorvastatin 80 mg/d would reduce the occurrence of death and non-fatal ischemic events.

Patients were included if they were at least 18 years of age, with prolonged chest pain within 24 hours of admission to hospital and objective evidence of ischemia (dynamic ECG changes, new wall motion abnormalities, new reversible ischemia on myocardial perfusion imaging, or elevation of cardiac troponin or CK/CKMB). Exclusion criteria were: total cholesterol > 7 mmol/L; planned or anticipated revascularization; Q-wave myocardial infarction within 4 weeks; coronary artery bypass surgery (CABG) within 3 months or percutaneous coronary intervention (PCI) within 6 months; a left bundle-branch block or paced ventricular rhythm; severe congestive heart failure (NYHA class IIIb or IV); concurrent therapy with lipid lowering agents (other than niacin at doses of 500 mg/d), vitamin E (except doses <400 IU/d), or drugs associated with the development of rhabdomyolysis in combination with statins; severe anemia; renal dialysis; hepatic dysfunction (ALT twice the upper limit of normal [ULN]); insulin-requiring diabetes; and pregnancy or lactation.

Patients were randomized to either atorvastatin 80 mg or placebo within 24-96 hours of admission, and then were followed for 16 weeks. The primary endpoint for the trial was the combined occurrence of death, nonfatal acute myocardial infarction (AMI), resuscitated cardiac arrest and recurrent symptoms with objective evidence of myocardial ischemia requiring readmission. Secondary endpoints were the occurrence of each primary endpoint component, as well as nonfatal stroke, new or worsening congestive heart failure (CHF) requiring hospitalization, worsening angina without objective evidence of ischemia requiring hospitalization, revascularization (CABG or PCI), time to first occurrence of any endpoint, and percentage change in lipids from baseline to the end of the study.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. From May 1997 to September 1999, 3086 patients were randomized (stratified by centre) to receive atorvastatin 80 mg/day or placebo. This article and a previous publication describing the rationale and design of the trial do not specifically address issues such as the number of patients screened, nor the specific details of randomization (i.e. on-site vs. centrally). (1)

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. A total of 3086 patients were enrolled, 1548 received placebo and 1538 received atorvastatin 80 mg/d. Withdrawal of study medication occurred in 10.4% of the placebo group and 11.4% of patients treated with atorvastatin. Analysis was conducted by a intention-to-treat strategy. Eleven patients were lost to follow-up. Patients who did not experience an endpoint were censored, with their survival time made to correspond to the day of final study contact.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. Local investigators were blinded, and all physicians involved in the care of the patients were asked not to perform serum lipid studies at local laboratories. All lipid measurements were done at a central laboratory. The endpoint adjudication committee, consisting of 6 cardiologists, was also blinded to treatment assignment of all patients.

4. Were the groups similar at the start of the trial?

Yes. Both groups of patients had similar baseline demographics, including serum lipid levels. They were also similar in terms of cardiovascular medication use prior to the index hospitalization.

5. Aside from the experimental intervention, were the groups treated

equally?

Yes. Both groups were managed similarly in terms of additional medical therapy after randomization. Open label lipid lowering agents were used in 3.0% of the placebo group and 2.0% of the atorvastatin group following the premature discontinuation of study medication. In addition, all patients received instruction to promote compliance with a National Cholesterol Education Program (NCEP) Step 1 diet.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

During the 16-week follow-up period, a primary end point occurred in 14.8% of the atorvastatin group and 17.4% of the placebo group ($p=0.48$), ARR = 2.6% (95% CI 0% to 5.2%), NNT = 38 (95% CI 20 to 11,893). There was no difference in the incidence of death, non-fatal MI, or resuscitated cardiac arrest between the two groups.

Recurrent symptoms with objective evidence of ischemia occurred in 6.2% of the atorvastatin group and 8.4% of the placebo group ($p=0.02$), ARR = 2.2% (95% CI 0.4% to 4%), NNT = 46 (95% CI 25 to 273). Non-fatal stroke occurred in 0.6% of the atorvastatin group and 1.4% of the placebo group ($p=0.02$, ARR = 0.8%, NNT=125) and either fatal or nonfatal stroke occurred in 0.8% of the atorvastatin group and 1.6% of the placebo group ($p=0.045$, ARR = 0.8%, NNT= 125). The NNT to prevent 1 primary end point event or nonfatal stroke was 33.

There were no interactions between treatment assignment and baseline demographic variables. During the course of follow-up, patients in the atorvastatin group experienced a 40% decline in serum LDL, and a 16% reduction in triglycerides, compared with increases of 12% and 9%, respectively, in the placebo group. No change in the HDL occurred in either group. However, the occurrence of an endpoint event was not related to baseline lipid levels, or to the changes in these levels.

There were no documented cases of myositis; however, 2.5% in the atorvastatin group experienced abnormal elevation of liver transaminases (ALT >3 times the upper limit of normal (ULN)) compared to 0.6% of the placebo group ($p<0.001$, ARI = 1.9%, NNH = 53).

2. How precise was the estimate of the treatment effect?

The combined primary endpoint was reduced from 17.4% in the placebo to 14.8% in the atorvastatin treated group ($p=0.049$). This endpoint just achieved statistical significance

at the a priori level of $p=0.049$ which was adjusted to preserve the overall type I error rate at $p=0.05$ with the 3 protocol interim analyses of safety and efficacy performed by the data safety monitoring board. While the 95% confidence intervals for the point estimate of the absolute risk reduction does not cross zero (i.e. the point of unity), the lower limit falls directly on zero. Consequently, the possibility exists that early intervention with atorvastatin 80 mg/d offers no benefit over placebo in reducing this primary combined endpoint. While the NNT for this endpoint appears to be acceptable, the 95% confidence interval around this point estimate are extremely wide (NNT = 38; 95% CI 20 to 11,893). Consequently, while atorvastatin treatment resulted in a statistically significant reduction in the primary endpoint, it is unclear whether or not it provides a clinically significant reduction in this endpoint.

This study was underpowered to detect differences between treatment groups for the individual components of the primary endpoint. Nevertheless, a statistically significant reduction in recurrent symptomatic ischemia requiring hospitalization was observed [$p = 0.02$], ARR = 2.2% (95% CI 0.4% to 4%), NNT = 46 (95% CI 25 to 273)]. This reduction in the secondary endpoint is what contributed to the main benefit observed for the primary endpoint. However, the 95% confidence intervals for this secondary event are narrow and the lower boundary includes a minimally important clinical difference.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. The broad range of lipid levels allowed in this trial would suggest general applicability. However, the patients enrolled in this study are at high risk of recurrent events on the basis of their presentation to hospital with either non-ST segment elevation MI, or unstable angina with objective evidence of ischemia. Recent literature supports an aggressive, early invasive management strategy for these patients, with angiography and revascularization if appropriate. (2, 3) Therefore, in contemporary clinical practice, the majority of these high-risk individuals would not have received the study intervention employed in the MIRACL trial. In the setting where there is no rapid access to a cardiac catheterization laboratory, it would be appropriate to consider initiation of statin therapy as demonstrated by the results of this study.

2. Were all clinically important outcomes considered?

Yes. All outcomes were clearly defined and are of significant importance.

3. Are the likely treatment benefits worth the potential harms and costs?

Yes. While the clinical significance of the reduction observed for the combined primary endpoint is unclear, early atorvastatin treatment provided both statistically and clinically significant reductions in a couple of secondary endpoints (recurrent symptomatic ischemia requiring hospitalization, non-fatal strokes and the combination of fatal and non-fatal strokes). No other secondary endpoints were significantly reduced by treatment with atorvastatin. In

addition, atorvastatin was generally well tolerated in this patient population. While there were no documented cases of myositis, elevations of serum transaminases (>3 times ULN) occurred in 2.5% of patient receiving atorvastatin patients compared to 0.6% of placebo treated patients ($p<0.001$). Also, 3 of the 38 atorvastatin treated patients with elevated liver enzymes were hospitalized with a diagnosis of hepatitis.

The long-term benefits of therapy with statin agents have already been proven in patients with coronary artery disease, and those at high risk to develop it. These agents are expensive, but provide considerable savings over time with regards to hospitalization and vascular morbidity and mortality. Nevertheless, the cost-effectiveness of early, short-term treatment with atorvastatin 80 mg/day for patients with acute coronary syndromes remains to be clarified.

Commentary

This trial involved the assessment of short-term drug administration in a high risk population of patients with ischemic heart disease. The most substantial benefit of these agents has been seen in trials of much longer duration (i.e. five to seven years), using different agents. Currently there is no evidence for long term morbidity and mortality benefit with the use of atorvastatin. The short term results in this underpowered study are certainly encouraging but further study is needed, both in the high risk patients who are treated with aggressive early invasive strategies, and for the long-term effects of atorvastatin on outcomes.

Even if we accept the beneficial role of early statin therapy for patients with and acute coronary syndrome, we are left with a number of unanswered questions. For example, can these results be extrapolated to contemporary clinical practice where a significant number of these patients undergo early coronary intervention (PCI) and/or receive a glycoprotein IIB/IIIA receptor antagonist? Can these results be extrapolated to patients with non-ST-segment myocardial infarctions (Q-wave MI's)? Would the same results occur with a lower dose of atorvastatin or another statin with proven long-term outcome benefits?

Methodological limitations and unanswered clinical questions notwithstanding, the results of this current trial should be viewed optimistically. vEven with only the potential for short-term benefits, our knowledge of the definite long-term benefits and absence of significant harm should provide sufficient evidence for all patients hospitalized for an acute coronary event to be initiated on a statin prior to their discharge. Prescribing lipid-lowering therapy with a statin in this manner may help to ensure that this important secondary prevention measure in not overlooked later in the patient's management. Additionally, initiating this therapy early may serve to emphasize to both the patient and their other primary care providers the importance of this treatment for cardiovascular risk reduction.

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6. Overall, are the results of the study valid?

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What were the Results?

1. How large was the treatment effect?

During the 16-week follow-up period, a primary endpoint occurred in 14.8% of the atorvastatin group and 17.4% of the placebo group ($p=0.48$), ARR = 2.6% (95% CI 0% to 5.2%), NNT = 38 (95% CI 20 to 11,893). There was no difference in the incidence of death, non-fatal MI, or resuscitated cardiac arrest between the two groups.

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2. How precise was the estimate of the treatment effect?

The combined primary endpoint was reduced from 17.4% in the placebo to 14.8% in the atorvastatin treated group ($p = 0.049$). This endpoint just achieved statistical significance at the a priori level of $p = 0.049$ which was adjusted to preserve the overall type I error rate at $p = 0.05$ with the 3 protocol interim analyses of safety and efficacy performed by the data safety monitoring board. While the 95% confidence intervals for the point estimate of the absolute risk reduction does not cross zero (i.e. the point of unity), the lower limit falls directly on zero. Consequently, the possibility exists that early intervention with atorvastatin 80 mg/d offers no benefit over placebo in reducing this primary combined endpoint. While the NNT for this endpoint appears to be acceptable, the 95% confidence interval around this point estimate are extremely wide (NNT = 38; 95% CI 20 to 11,893). Consequently, while atorvastatin treatment resulted in a statistically significant reduction in the primary endpoint, it is unclear whether or not it provides a clinically significant reduction in this endpoint.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;7:208-212.

Beta-Blockers in Congestive Heart Failure: What Can We Learn from a Bayesian Meta-Analysis?

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Risk Reduction

Original Citation

Brophy JM, Joseph L, Rouleau JL. Beta-Blockers in congestive heart failure: a Bayesian meta-analysis. Ann Intern Med 2001;134:550-560. [PubMed Citation](#)

Overall Study Question

Congestive heart failure (CHF) is a common syndrome characterized by exceedingly high rates of morbidity and mortality. In Canada, there are reportedly more than 350,000 persons afflicted with the condition, and the mortality rate one year after diagnosis ranges between 25-40%. (1) In addition, CHF is the leading single indication for admission to the hospital among elderly Canadians. (1) Accumulated evidence from published randomized control trials demonstrates that effective treatment strategies (angiotensin-converting enzyme inhibitors (ACEI), digoxin and spironolactone) are available to improve both quantity and quality of life of patients with CHF. Definitive evidence for the use of beta-blockers in CHF has also emerged in the last few years. This evidence is in direct contrast to conventional medical teaching, which viewed CHF as a contraindication to beta-blocker therapy due to the propensity for this class of drugs to exert negative inotropic effects in the short-term. Consequently, there exists a care gap between the research evidence and clinical practice for the use of beta-blockers in patients with CHF.

The present investigation was a meta-analysis of published randomized control trials that involved a comparison of beta-blockers with placebo in patients with CHF, quantifying the effect of treatment on morbidity and mortality. While no less than four meta-analyses of randomized control trials with beta-blockers in CHF have previously been published, the present study is unique for two reasons. Firstly, the previous meta-analyses were published a few years ago and since that time, additional large trials

with beta-blockers in CHF have been published. Secondly, unlike previous meta-analyses that used a “fixed-effects model”, the present study employed a “Bayesian hierarchical random-effect model”. This novel method of meta-analysis has several advantages, including the ability to account for between-study variation.

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1. Did the overview address a focused clinical question?

Yes. The investigators performed a meta-analysis of the cumulative experience of beta-blockers compared to placebo in patients with heart failure from randomized control trials published prior to July 2000.

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Yes. The investigators defined the criteria for study selection a priori and included all randomized clinical trials of beta-blockers versus placebo in chronic stable CHF that evaluated mortality as an outcome. Trials were excluded if they involved: 1) cross-over designs; 2) beta-blockers with intrinsic sympathomimetic activity (ISA); 3) a follow-up period of <3 months, or; 4) patients admitted for acute myocardial infarction. Twenty-two randomized controlled trials published between 1985 and 2000 fulfilled the criteria for inclusion in this meta-analysis.

3. Is it unlikely that important, relevant studies were missed?

Yes. The investigators searched the MEDLINE database from 1966 to July 2000 using the keywords adrenergic beta-antagonists, congestive heart failure, and trial to identify relevant studies. This initial approach identified 105 trials, of which 17 met the inclusion criteria. Subsequently, they examined the references cited in the four meta-analyses previously published in 1987 and 1988 to find an additional 5 trials that were appropriate for inclusion. The final step undertaken to identify pertinent trials was a search of the Cochrane and Web of Science databases. This process did not reveal any additional trials.

4. Was the validity of the included studies appraised?

Yes. Each of the 22 randomized controlled trials included in this meta-analysis followed a double-blind protocol, with only one study reported as having possible irregularities in the randomization process. For all of the studies, the follow-up of randomly assigned patients was almost complete. The investigators commented that the only minor methodological flaw in the studies was a lack of description of the randomization process in 18 of the 22 trials included.

5. Were assessments of studies reproducible?

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inclusion in the meta-analysis, nor did they comment as to whether or not agreement between two or more of the investigators was required for a study to be included.

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What were the Results?

1. What are the overall results of the review?

There were 110 studies identified, however only 22 studies (involving 10,135 patients) met the inclusion criteria for meta-analysis. The observed mortality rate among placebo treated patients was 12.8% (624/4862) and 8.4% (444/5273) for patients treated with a beta-blocker. The combined odds ratio (OR) for total mortality among all patients in the studies was 0.65 (95% credible interval, 0.53 to 0.80). Utilizing the hierarchically determined mortality rate of 12% (credible interval, 4% to 26%) in the first year of follow-up among placebo treated patients from the 3 largest and most recent trials, the best estimate of the absolute mortality reduction during the first year of treatment was 3.8 lives saved per 100 patients treated (credible interval, 2.1 to 5.3). From the Bayesian analysis derived probability density curve, the probability that beta-blocker therapy saves at least 2 lives per 100 patients in the first year of treatment is 99% and the probability that 3 or more lives are saved per 100 patients over this timer period is 85%.

While various beta-blockers were evaluated in the individual randomized control trials (8 trials of metoprolol, 8 of carvedilol, 3 of bucindolol, 2 of bisoprolol, and 1 of nebivolol), the mortality benefit observed with selective agents (metoprolol, bisoprolol) and non-selective agents (carvedilol, bucindolol) was similar (OR 0.67 (credible interval, 0.57 to 0.79) and OR 0.52 (credible interval, 0.28 to 0.89), respectively).

Beta-blocker therapy was also associated with a reduction in morbidity in these trials. Seven hundred and fifty-four of 4862 (15.5%) placebo recipients were hospitalized for heart failure as compared with 540 of 5273 (10.2%) beta-blocker recipients. The combined odds ratio for hospitalization for CHF was 0.64 (credible interval, 0.53 to 0.79). Based on trials published since 1996, the weighted average of admissions for CHF among placebo recipients in the first year of follow-up was 14%. This translated into a best estimate of 4.0 fewer hospitalizations per 100 patients treated with a beta-blocker (credible interval, 2.4 to 5.6). From the Bayesian analysis derived probability density curve, the probability that beta-blocker therapy prevents at least 2 hospital admissions for CHF per 100 patients 99% and the probability that 3 or more hospital admissions for CHF are prevented per 100 patients is 90%.

2. How precise were the results?

The results of this meta-analysis are statistically significant in favour of beta-blocker therapy as compared to placebo for all outcomes analyzed. The Bayesian hierarchical random-effect model utilized for this meta-analysis generated “credible intervals”, the Bayesian analogue to 95% confidence intervals, as a measure of precision. For all of the outcomes evaluated, the “credible intervals” were provided in the text. The combined odds ratios for total mortality and hospital admissions for heart failure were statistically significant since the credible intervals did not cross 1.0 (the point of unity). In addition, since the credible intervals around the point estimate were narrow and the lower boundaries of these intervals represent minimal clinically important differences, these results can be considered clinically significant.

3. How much does allowance for uncertainty change the results?

In the sensitivity analysis, the investigators considered an extreme situation in which further trials involving 2,000 patients with mortality rates of 20% in the beta-blocker treated patients (200/1,000) and 10% in the placebo treated patients (100/1,000) were included in the meta-analysis. Inclusion of this hypothetical negative data in the meta-analysis revealed an OR of 0.84 (credible interval, 0.74 to 0.94). This result would still support the finding that beta-blockers reduce the odds ratio of mortality from CHF by 16%. This sensitivity analysis demonstrates the robustness of the findings from this study and the probability that they will hold up to possibly unfavourable future or unpublished results. The investigators also comment that the Bayesian method of meta-analysis can be easily repeated and updated to allow for inclusion of new trial data. They used the preliminary results of the Beta-blockers Evaluation Survival Trial (BEST) presented at the 72nd Scientific Sessions of the American Heart Association (2), as an example. In this randomized control trial of 2,708 patients, the mortality rate after 2 years of follow-up was 33% in the placebo group and 30.2% in the bucindolol treated group. Incorporation of these results into the meta-analysis revealed an accumulated OR of 0.72 (credible interval, 0.61 to 0.84). Finally, an additional analysis performed for the mortality benefit observed with beta-blockers categorized according to their adrenergic receptor selectivity revealed consistent results. The OR was 0.67 for selective agents (credible interval, 0.57 to 0.79) and the OR was 0.52 for non-selective agents (credible interval, 0.28 to 0.89).

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

CHF is a common syndrome characterized by exceedingly high rates of morbidity and mortality despite the utilization of effective pharmacotherapeutic strategies, such as ACE-I's, digoxin and spironolactone. This meta-analysis demonstrates that beta-blockers have a large beneficial effect on mortality (3.8 lives per 100 patients treated) and morbidity (4.0 fewer hospitalizations per 100 patients treated) in stable NYHA class II or III CHF. The benefits of beta-blockers in CHF go beyond those provided by ACEI since the majority of patients were receiving an ACEI at the

time of randomization. In addition, most patients were also receiving diuretics and digoxin at the time they were randomized to receive treatment with a beta-blocker.

2. Were all clinically important outcomes considered?

Mortality is a hard endpoint and the ultimate goal of CHF pharmacotherapy is to reduce overall mortality. Additionally, hospitalization for CHF is a clinically relevant morbidity endpoint that is targeted for reduction with current pharmacotherapy.

3. Are the likely treatment benefits worth the potential harms and costs?

The reductions in mortality (3.8 lives per 100 patients treated) and hospitalizations for heart failure (4.0 fewer hospitalizations per 100 patients treated) observed in this meta-analysis are clinically important. The initiation of beta-blocker therapy is not without toxicity. The potential for short-term deterioration in clinical status (e.g. dizziness, hypotension and worsening CHF) of patients during the initiation and titration of the beta-blocker is a frequent problem. This is confirmed by the 5% withdrawal rate observed in the run-in periods of the clinical trials. Nevertheless, if the patients are informed of this potential and physicians carefully supervise the initiation of beta-blocker therapy in their patients, the short-term "pain" appears to result in significant long-term gain. While the cost-effectiveness of beta-blocker therapy in the treatment of CHF was not assessed in this study (and remains to be analyzed formally), the investigators do comment that the large treatment benefits and low cost of therapy indicate that it will be cost attractive.

Commentary

This meta-analysis provides further support for the recommendations made in recent consensus conferences [3, 4] that strongly suggest the use of beta-blockers in all patients with NYHA class II-III heart failure. This study also builds on our previous knowledge of the effect of beta-blockers in CHF from the 4 previously published meta-analyses, with the inclusion of the results from more recent large trials. Of interest, before 1999 only 3,071 patients were randomized in the trials of beta-blockers in CHF and this number had increased to 10,135 by July 2000. The results of the present study are reported as odds ratios (OR), which are the traditional means for reporting treatment effects in a meta-analysis. One limitation of reporting OR is the fact that they fail to account for absolute differences. Consequently, OR may obscure the true clinical significance of an intervention. In this study, the investigators used the Bayesian hierarchical random-effect model specifically to avoid this problem. With Bayesian analysis, probability density distributions of the differences in survival and hospitalization at 1 year between patients receiving beta-blockers and placebo were created. Subsequently, direct probability estimates to pertinent questions were calculated by measuring the area under the curve (AUC). Most clinicians will not necessarily be familiar with probability density distributions; however, be assured that they are "clinically friendly" since they supply direct probability estimates to multiple questions. This method permits the calculation of probabilities that relate to any interval null or alternative hypotheses, as well as any range of clinically meaningful effects. Consequently, this Bayesian method provides for clearer clinical interpretations of the accumulated data.

The present study demonstrates that beta-blocker therapy is associated with significant and clinically

meaningful reductions in mortality (3.8 lives per 100 patients treated) and hospitalizations for heart failure (4.0 fewer hospitalizations per 100 patients treated). These results are limited to clinically stable patients with NYHA class II or III CHF treated with either selective or non-selective beta-blockers. The role of beta-blocker therapy in patients with NYHA class IV CHF remains uncertain and cannot be extrapolated from these results since this population accounts for <5% of the patients studied to date. While large mega-trials will be required to detect whether any clinically significant difference exists between beta-blockers in CHF, this meta-analysis should provide clinicians with the impetus to use beta-blockers for the treatment of all eligible patients with CHF. Eligible patients receiving standard triple drug therapy for CHF (diuretics, digoxin, and ACE-I) should be initiated with low doses (e.g., 6.25-12.5 mg of metoprolol, 3.125 mg of carvediolol, or 2.5 mg of bisoprolol) and titrated slowly under the close monitoring of a health professional. Judicious monitoring of patients for clinical deterioration and appropriate management of such symptoms (dizziness, hypotension and worsening CHF) will ensure that they adhere to therapy and derive the significant clinical benefits that are possible with beta-blocker therapy.

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Beta-Blockers in Congestive Heart Failure: What Can We Learn from a Bayesian Meta-Analysis?

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Reviewer's profession/specialty: Assistant Professor of Medicine; Cardiology/Cardiac Transplantation/Risk Reduction

Original Citation

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2001;7:213-216.

IIb or not IIb: That is the question, but what is the TARGET?

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Original Citation

Topol EJ, Moliterno DJ, Herrmann HC, Powers ER, Grines CL, Cohen DJ, Cohen EA, Bertrand M, Neumann F, Stone GW, DiBattiste PM, Demopoulos L, for the TARGET investigators. A comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. N Engl J Med 2001;344:1888-94. [PubMed Citation](#)

Overall Study Question

The TARGET (Do Tirofiban and Reopro Give Similar Efficacy Outcomes Trial) trial was designed to compare the efficacy and safety of two glycoprotein IIb/IIIa antagonists, tirofiban and abciximab, in patients scheduled to undergo urgent or elective coronary stenting who possessed new or restenotic atherosclerotic lesions and either native or bypass grafts. Previous studies involving the individual glycoprotein IIb/IIIa antagonists have demonstrated the clinical benefit of these individual agents for use in percutaneous coronary interventions, however, no study has compared whether clinical differences between agents exist for this indication. (1-7)

The primary hypothesis in this study was that tirofiban would not be inferior to abciximab in regards to the primary endpoint. The primary endpoint of this study was a composite of death, non-fatal infarction, or urgent target vessel revascularization within 30 days after the procedure. Secondary outcomes were each component of the primary endpoint and the effect of the medications on the following subgroups: presence or absence of diabetes, sex, age (< 65 years or ≥65 years), country (US versus other), and whether or not clopidogrel was administered prior to the procedure.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Immediately prior to the procedure, patients were randomized to tirofiban or abciximab. Tirofiban was administered as a bolus of 10 ug/kg, followed by an infusion of 0.15 ug/kg/min for 18-24 hours. Abciximab was administered as a 0.25 mg/kg bolus, followed by a 0.125 ug/kg/min infusion for 12 hours. All patients received heparin at least 4 hours prior to the procedure, and at a maximum dose of 70 u/kg to achieve a target activated clotting time of 250 seconds. It was recommended that heparin be discontinued immediately after the procedure. Additionally, all patients received 250 mg to 500 mg of aspirin and a 300 mg load of clopidogrel two to six hours prior to the procedure. Both agents (75 mg-325 mg for aspirin and 75 mg for clopidogrel) were continued for 30 days after the procedure.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

There were 5,308 patients enrolled (2647 randomized to tirofiban and 2661 to abciximab). The protocol specified that patients would be excluded from the analysis if they did not actually receive a study drug. Two hundred and forty-nine (9%) patients randomized to receive tirofiban and 250 (9%) patients randomized to receive abciximab were excluded for this reason. There were 4,809 patients (2,398 in the tirofiban group and 2,411 in the abciximab group) ultimately evaluated for the primary endpoint.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. Treatment was assigned and administered in a double-blinded, double-dummy manner. An independent committee of cardiologists who were unaware of the patients' treatment assignment were responsible for evaluating the endpoints. Endpoints were confirmed after two cardiologists evaluated the data and came to a consensus. In the event that the two physicians did not agree, a third cardiologist was asked to make the final decision.

4. Were the groups similar at the start of the trial?

Yes. The baseline characteristics for both groups were similar in regards to age, sex, risk factors for heart disease, and past medical history. Ninety-five percent of patients underwent stenting and 95% of the lesions involved native coronary vessels.

5. Aside from the experimental intervention, were the groups treated equally?

There were no obvious treatment differences between groups reported in the study. The mean dose of heparin was 6,327 U in the tirofiban group and 6,372 U in the abciximab group.

What were the Results?

1. How large was the treatment effect?

The study was designed to be an equivalence trial, with a pre-set primary hypothesis that tirofiban would not be inferior to abciximab. The results rejected the primary hypothesis. The authors then went on to determine whether or not tirofiban was superior to abciximab.

The 30-day primary endpoint was met in 7.6% of patients in the tirofiban group and 6% in the abciximab group, $p=0.038$. This translates into a 27% relative risk reduction in the abciximab group or a number needed to treat (NNT) of 63 patients treated with abciximab, infused for 12 hours, and aspirin and clopidogrel administered for 30 days. The difference was primarily due to a reduction in nonfatal myocardial infarctions, especially larger infarctions. These events occurred in 6.9% of patients in the tirofiban group, and 5.4% of patients in the abciximab ($p=0.04$).

The beneficial effects of abciximab were consistent for all patient subgroups. Significant decreases in the primary endpoint occurred in the sub-group of patients who were < 65 years of age, female, or being treated in centers outside the United States.

There were no significant differences in the major bleeding rates between the two groups. Minor bleeding rates were significantly lower in the tirofiban group (2.8%) compared to the abciximab group (4.3%), $p=0.001$. Furthermore, thrombocytopenia occurred significantly more often with abciximab than with tirofiban. There were no differences between groups in the need for red-cell or platelet transfusions.

2. How precise was the estimate of the treatment effect?

The 95% confidence interval for the primary endpoint was 1.01 to 1.57 ($p=0.038$). The 95% confidence interval for the secondary outcomes of nonfatal myocardial infarction, treatment in patients < 65 years, female, and patients treated at medical centers outside the United States did not cross zero, indicating statistically significant differences.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

This study indicates that treatment of patients undergoing elective or urgent percutaneous interventions with stenting derive greater benefit from treatment with abciximab than from tirofiban.

2. Were all clinically important outcomes considered?

The investigators evaluated the important clinical outcomes of death, nonfatal myocardial infarction, and the need for target vessel revascularization at 30 days and

found a significant decrease in patients treated with abciximab. Whether these results would be similar beyond 30 days is unclear.

It should be noted that although the entry criteria for the study included patients requiring stenting of bypass grafts, the majority (95%) of patients entered into the study underwent stenting of a native vessel. Whether the results would have been different had more patients with bypass grafts been enrolled requires further study.

This study evaluated the incidence of adverse events between the two agents. The higher incidence of minor bleeding and thrombocytopenia with abciximab was consistent with previous abciximab studies.

3. Are the likely treatment benefits worth the potential harms and costs?

This trial addressed important clinical outcomes in patients undergoing elective or urgent percutaneous interventions. Although the cost of abciximab is higher than that of tirofiban (approximately \$1277 for a bolus and 12-hour infusion of abciximab vs. \$399 for a bolus and 24-hour infusion of tirofiban, for a 70-kg person), this study suggests that abciximab is a more efficacious than is tirofiban for use in percutaneous interventions. Formal cost-effective analysis comparing these two agents and their outcomes are necessary.

Commentary

The development of percutaneous coronary interventions, such as angioplasty (PTCA) alone or with stent placement, has revolutionized the management of patients with ischemia by reducing symptoms, improving clinical outcomes and enhancing patients' quality of life. Nevertheless, the use of these procedures can result in acute vessel closure in approximately 4-9% of cases, resulting in increased mortality. (8) The use of glycoprotein IIb/IIIa receptor antagonists prior to and during PTCA have been shown to reduce death, nonfatal myocardial infarctions and the need for repeat percutaneous coronary interventions, although to date no study has evaluated the impact of these agents on all-cause mortality. (1-7) The use of these agents are now routine during percutaneous coronary interventions.

The TARGET trial is the first published study designed to directly compare the efficacy and safety of two glycoprotein IIb/IIIa receptor antagonists, abciximab and tirofiban. The results of the TARGET trial indicate that the use of abciximab is superior to that of tirofiban in preventing death, nonfatal myocardial infarctions, or urgent target-vessel revascularization within 30 days after the procedure. It should be noted that the infusion duration for tirofiban used in this study was shorter than that used in the original study that demonstrated the clinical benefit of using tirofiban in percutaneous interventions. (5) The choice in therapy duration for the study was chosen based upon the results of a sub-group analyses from a study evaluating tirofiban for patients with unstable angina or non-Q-wave myocardial infarctions. (9) Whether this difference had an impact on the results of the current trial remains unknown.

Further investigations into whether differences between the other IIb/IIIa antagonists exist are warranted, not only in the setting of coronary interventions but also in the setting of acute coronary syndromes.

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IIb or not IIb: That is the question, but what is the TARGET?

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Original Citation

Topol EJ, Moliterno DJ, Herrmann HC, Powers ER, Grines CL, Cohen DJ, Cohen EA, Bertrand M, Neumann F, Stone GW, DiBattiste PM, Demopoulos L, for the TARGET investigators. A comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med* 2001;344:1888-94.

Overall Study Question

The TARGET (Do Tirofiban and Reopro Give Similar Efficacy Outcomes Trial) trial was designed to compare the efficacy and safety of two glycoprotein IIb/IIIa antagonists, tirofiban and abciximab, in patients scheduled to undergo urgent or elective coronary stenting who possessed new or restenotic atherosclerotic lesions and either native or bypass grafts. Previous studies involving the individual glycoprotein IIb/IIIa antagonists have demonstrated the clinical benefit of these individual agents for use in percutaneous coronary interventions, however, no study has compared whether clinical differences between agents exist for this indication. (1-7)

The primary hypothesis in this study was that tirofiban would not be inferior to abciximab in regards to the primary endpoint. The primary endpoint of this study was a composite of death, non-fatal infarction, or urgent target vessel revascularization within 30 days after the procedure. Secondary outcomes were each component of the primary endpoint and the effect of the medications on the following subgroups: presence or absence of diabetes, sex, age (< 65 years or ≥65

years), country (US versus other), and whether or not clopidogrel was administered prior to the procedure.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Immediately prior to the procedure, patients were randomized to tirofiban or abciximab. Tirofiban was administered as a bolus of 10 ug/kg, followed by an infusion of 0.15 ug/kg/min for 18-24 hours. Abciximab was administered as a 0.25 mg/kg bolus, followed by a 0.125 ug/kg/min infusion for 12 hours. All patients received heparin at least 4 hours prior to the procedure, and at a maximum dose of 70 u/kg to achieve a target activated clotting time of 250 seconds. It was recommended that heparin be discontinued immediately after the procedure. Additionally, all patients received 250 mg to 500 mg of aspirin and a 300 mg load of clopidogrel two to six hours prior to the procedure. Both agents (75 mg-325 mg for aspirin and 75 mg for clopidogrel) were continued for 30 days after the procedure.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

There were 5,308 patients enrolled (2647 randomized to tirofiban and 2661 to abciximab). The protocol specified that patients would be excluded from the analysis if they did not actually receive a study drug. Two hundred and forty-nine (9%) patients randomized to receive tirofiban and 250 (9%) patients randomized to receive abciximab were excluded for this reason. There were 4,809 patients (2,398 in the tirofiban

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group and 2,411 in the abciximab group) ultimately evaluated for the primary endpoint.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. Treatment was assigned and administered in a double-blinded, double-dummy manner. An independent committee of cardiologists who were unaware of the patients' treatment assignment were responsible for evaluating the endpoints. Endpoints were confirmed after two cardiologists evaluated the data and came to a consensus. In the event that the two physicians did not agree, a third cardiologist was asked to make the final decision.

4. Were the groups similar at the start of the trial?

Yes. The baseline characteristics for both groups were similar in regards to age, sex, risk factors for heart disease, and past medical history. Ninety-five percent of patients underwent stenting and 95% of the lesions involved native coronary vessels.

5. Aside from the experimental intervention, were the groups treated equally?

There were no obvious treatment differences between groups reported in the study. The mean dose of heparin was 6,327 U in the tirofiban group and 6,372 U in the abciximab group.

What were the Results?

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Issues in Pharmacotherapy Practice

SSRI Discontinuation Syndrome

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J Inform Pharmacother 2001;7:303-304

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In recent years, it has become apparent that withdrawal of selective serotonin reuptake inhibitors (SSRIs) may produce an acute "discontinuation syndrome" in up to 30% of patients who reduce or discontinue therapy. (1)

Several of the signs and symptoms of this syndrome overlap with those of depression and thus it is important to differentiate between SSRI withdrawal phenomena and relapsing depressive illness. Recently, a series of case reports were utilized to compile diagnostic criteria, intended to aid in clinical diagnosis of the syndrome. The criteria state that two or more of the following symptoms (dizziness, light-headedness, vertigo or feeling faint; shock-like sensations or paresthesia; anxiety; diarrhea; fatigue; gait instability; headache; insomnia; nausea or emesis; tremor; and visual disturbances) developing within 1 to 7 days of discontinuation or reduction in dosage, after at least 1 month's use of an SSRI, causing clinically significant distress or impairment and not due to a general medical condition or recurrence of a mental disorder are indicative of the syndrome. (2)

Although the exact mechanism of syndrome development remains a mystery, it has been proposed that long-term administration of an SSRI increases the amount of available serotonin exposed to receptors (due to blockade of the serotonin reuptake pump). This may ultimately cause down regulation of these receptors and tolerance to unwanted side effects. (1) Once the SSRI is reduced or discontinued there may be a decrease in available serotonin concentrations at these receptor sites, leading to a deficiency of serotonin in the synapse. (1) This temporary "lack" of serotonin (lasting from 48 hours-10 days) combined with receptor down regulation may correspond with the onset of

symptoms characteristic of the syndrome. (1)

The severity and frequency of the syndrome differs among SSRIs, with variation being attributed to differing pharmacokinetic profiles, more specifically to the individual half-lives and existing metabolites of the drugs. Fluoxetine, which has a half-life of 24 hours and an active metabolite (norfluoxetine) with a half-life of 7 days, causes fewer adverse events upon treatment interruption than paroxetine, which has a half-life of 21 hours and no active metabolite. (3) Therefore, SSRIs with short elimination half-lives or those without active metabolites are more likely to cause a discontinuation syndrome due to more rapid systemic clearance of the drug from the body. (4) Hence, the clinical advantages and disadvantages of using an SSRI with a long half-life and/or presence of an active metabolite with a long half-life should be considered in individual situations. (5)

Two treatment options exist in terms of clinical management of the syndrome. The drug or previous dosage can be restarted, producing relatively rapid symptom resolution in true withdrawal situations, keeping in mind that 75% of patients experience recurring discontinuation symptoms on future withdrawal attempts. (2) Alternatively, the syndrome can be allowed to "run its course" while the patient is provided with supportive counseling and reassurance of eventual symptom resolution. (2)

Although most case reports of the discontinuation syndrome have been mild to moderate in nature, these incidents do pose potential complications for those recovering from a depressive episode. (5) The frequency of the SSRI discontinuation syndrome necessitates awareness by clinicians and patients alike. A gradual taper of SSRIs with short elimination half-lives should be considered whenever the clinical situation permits, as it may minimize the potential for inducing this syndrome.

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Issues in Pharmacotherapy Practice

Education, Illustrations and Antidepressant Treatment Compliance

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J Inform Pharmacother 2001;7:300-302

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Introduction

It is well established that although prevalent, chronic, and treatable, depression remains significantly under recognized and under treated. (1) Improving the ability to recognize and adequately treat depression, at the level of the public and the clinician, is a formidable challenge with comprehensive efforts making little headway. (2,3) When depression is diagnosed and treated, the next challenge is to provide that treatment in a manner that will optimize the chance for a full response. Implicit here is that the treatment is adhered to by the patient and that non-compliance predicts a poor outcome.

Compliance specific to antidepressant therapy, which is usually intended for 4-12 (or more) consecutive months, (4,5) is inadequate in general. Separate trials have observed that at 3 months 60-68 percent of antidepressant users interrupt their treatment course prematurely, apparently independent of which antidepressant is prescribed. (6,7) Surmountable causes, including misconceptions and misguided expectations regarding antidepressant therapy and a lack of understanding of the course of illness, have contributed to poor treatment compliance. (7) To overcome this, simple interventions such as the provision of patient leaflets about antidepressant drug therapy have failed to stem the tide of treatment non-compliance, as was demonstrated by Peveler et al in a randomized controlled trial. (8) However, verbal counseling was associated with improved adherence.

Experience from the Depression Treatment and Research Program at the University of Pittsburgh, which include the completion of landmark controlled trials of long-term pharmacologic and psychotherapeutic interventions, has identified several factors important in optimizing treatment adherence. These include a multidisciplinary approach, education of patients and family about depression and its treatments, and a philosophy and approach that emphasizes alliance rather than compliance. (9)

Visual aid to improve compliance

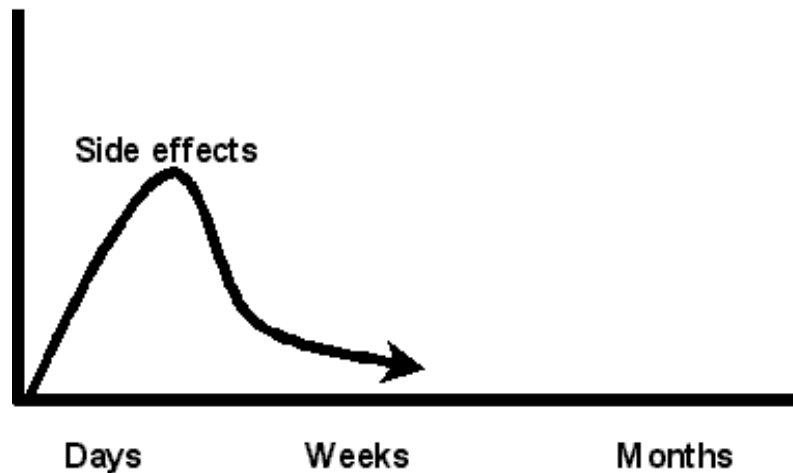
Offered here is a relatively simple and time efficient educational tool that I have used with individuals starting antidepressant treatment that conforms to the compliance-enhancing principles expressed by the researchers at the Pittsburgh program. The tool facilitates educating the patient about what to expect during the acute phase of antidepressant therapy and emphasizes the importance of long-term treatment adherence. The approach is specifically intended to minimize the number of avoidable premature treatment discontinuations, such as due to a lack of response early in the course of therapy or the development of side effects without any benefits, as revealed by Maddox et al. (7) In addition, it encourages an educational discussion with the patient about depression and the role of antidepressant therapy.

There are several methods of providing patients with this illustration. It is important to be flexible and adjust the information based on the patient's educational needs. From my experience, the most effective method is to build the figures freehand on blank paper adding the components and comments of each while giving a simultaneous verbal orientation. This allows for of any relevant, patient-specific information to be included. However, this approach does take a little more practice and experience. Depending on the situation, panels 1-3 usually are completed using the same axis. Panel 4 is often drawn at a later visit when the importance of adherence during the continuation phase is being emphasized. A simpler method is to provide a copy of the illustration (usually panel 3) and describe the components verbally with notes added onto the illustration as needed. It is not known if creating the illustration for a patient vs. providing them with a ready-made version differentially affects their treatment compliance or chance for response. Relapse probably should be addressed by a separate illustration if providing patients with a ready-made illustration. Regardless of which method is used, adding the patient's name and medication (drug and brand) names further personalizes this communication and enhances its impact.

The following points outline the components of the illustration with verbal descriptions

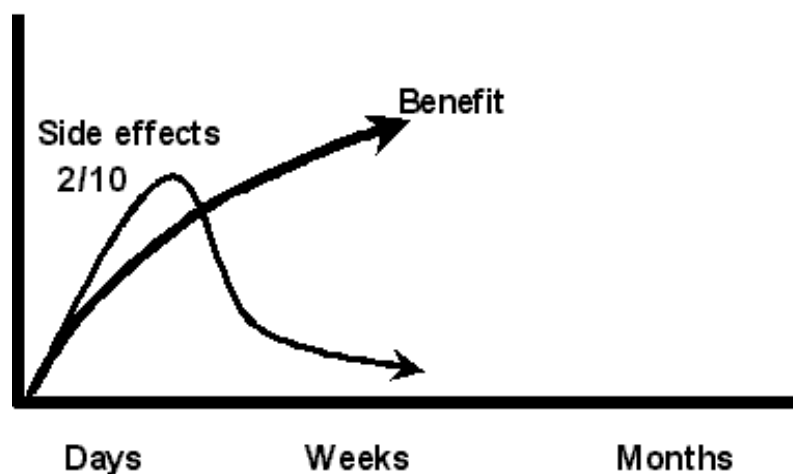
offered. The quantitative data were collectively derived and simplified from practice guidelines and randomized controlled trials (RCTs). The data represent the more optimistic end of the spectrum of RCT findings but may be achievable in general practice when the proper expectations are set and supports are in place.

Panel 1:



- Early in treatment, side effects can occur and can predominate over perceived benefits. However, for most people (~8/10) the side effects are tolerable and resolve within the first few days or weeks of treatment. Some individuals (~2/10) do stop treatment because of side effects early in therapy.

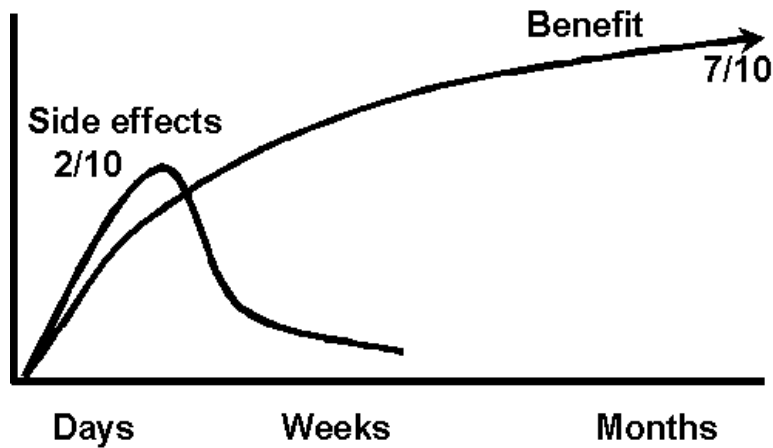
Panel 2:



- For many, the benefits of antidepressant therapy are not appreciated until several weeks of treatment have passed. Most individuals notice

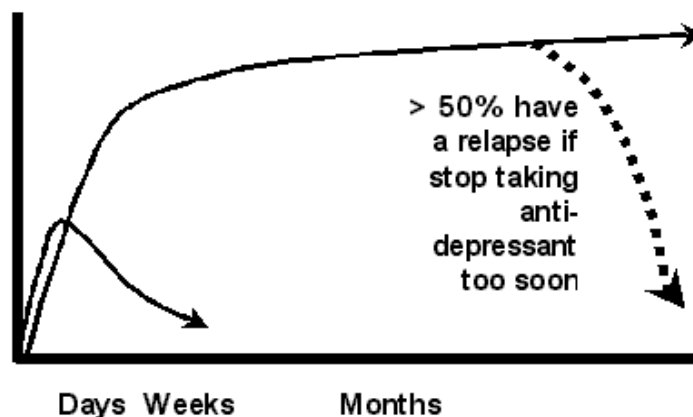
that they are beginning to feel better at around 4 weeks but continue to improve with therapy well beyond that time.

Panel 3:



- Nearing 8 weeks, approximately 7 people out of 10 who start therapy with an antidepressant achieve a good response and approximately 5 will have complete resolution of their symptoms of depression.
- Unfortunately, 3 out of 10 people do not achieve the desired benefits from treatment, whether because of side effects or lack of response or a mixture of factors. · It is not possible to determine prior to starting therapy who will respond (a 7 in 10 chance) versus who will not respond adequately (3 in 10 chance).
- If a good response does not occur there are other effective treatments available.

Panel 4:



- Due to the nature of the underlying depressive episode, stopping therapy too early is associated with a return of depressive symptoms in

more than 50% of people, even if they have had a very good response to treatment

- Once a good response has been achieved, treatment should continue as directed, which is commonly 6 months or more.

Admittedly, my evaluation of this teaching tool is anecdotal, derived from my experience and others who I have been able to influence to use it likewise. However, I have found that for patients unaccustomed to treatment with antidepressants, the effect of the message conveyed by the illustration along with a complementary verbal discussion can have a profound effect on their comfort and willingness at the start of treatment. It has also been effective in educating family members about the role of antidepressant treatment, leading to a therapeutic alliance that goes beyond the patient.

In their systematic review of medication compliance in chronic diseases, Haynes et al noted that current methods of improving adherence are mostly complex and not very effective. (10) The illustration described here is simple, efficient and promotes the development of a therapeutic alliance.

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Issues in Pharmacotherapy Practice

Education, Illustrations and Antidepressant Treatment Compliance

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J Inform Pharmacother 2001;7:300-2.
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It is well established that although prevalent, chronic, and treatable, depression remains significantly under recognized and under treated. (1) Improving the ability to recognize and adequately treat depression, at the level of the public and the clinician, is a formidable challenge with comprehensive efforts making little headway. (2,3) When depression is diagnosed and treated, the next challenge is to provide that treatment in a manner that will optimize the chance for a full response. Implicit here is that the treatment is adhered to by the patient and that non-compliance predicts a poor outcome.

Compliance specific to antidepressant therapy, which is usually intended for 4-12 (or more) consecutive months, (4,5) is inadequate in general. Separate trials have observed that at 3 months 60-68 percent of antidepressant users interrupt their treatment course prematurely, apparently independent of which antidepressant is prescribed. (6,7) Surmountable causes, including misconceptions and misguided expectations regarding antidepressant therapy and a lack of understanding of the course of illness, have contributed to poor treatment compliance. (7) To overcome this, simple interventions such as the provision of patient leaflets about antidepressant drug therapy have failed to stem the tide of treatment non-compliance, as was demonstrated by Peveler et al in a randomized controlled trial. (8) However, verbal counseling was associated with improved adherence.

Experience from the Depression Treatment and Research Program at the University of Pittsburgh, which include the completion of landmark controlled trials of long-term pharmacologic and psychotherapeutic interventions, has identified several factors important in optimizing treatment adherence. These include a multidisciplinary approach, education of patients and family about depression and its treatments, and a philosophy and approach that emphasizes alliance rather than compliance. (9)

Visual aid to improve compliance

Offered here is a relatively simple and time efficient educational tool that I have used with individuals starting antidepressant treatment that conforms to the compliance-enhancing principles expressed by the researchers at the Pittsburgh program. The tool facilitates educating the patient about what to expect during the acute phase of antidepressant therapy and emphasizes the importance of long-term treatment adherence. The approach is specifically intended to minimize the number of avoidable premature treatment discontinuations, such as due to a lack of response early in the course of therapy or the development of side effects without any benefits, as revealed by Maddox et al. (7) In addition, it encourages an educational discussion with the patient about depression and the role of antidepressant therapy.

There are several methods of providing patients with this illustration. It is important to be flexible and adjust the information based on the patient's educational needs. From my experience, the most effective method is to build the figures freehand on blank paper adding the components and comments of each while giving a simultaneous verbal orientation.

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This allows for of any relevant, patient-specific information to be included. However, this approach does take a little more practice and experience. Depending on the situation, panels 1-3 usually are completed using the same axis. Panel 4 is often drawn at a later visit when the importance of adherence during the continuation phase is being emphasized. A simpler method is to provide a copy of the illustration (usually panel 3) and describe the components verbally with notes added onto the illustration as needed. It is not known if creating the illustration for a patient vs. providing them with a ready-made version differentially affects their treatment compliance or chance for response. Relapse probably should be addressed by a separate illustration if providing patients with a ready-made illustration. Regardless of which method is used, adding the patient's name and medication (drug and brand) names further personalizes this communication and enhances its impact.

The following points outline the components of the illustration with verbal descriptions offered. The quantitative data were collectively derived and simplified from practice guidelines and randomized controlled trials (RCTs). The data represent the more optimistic end of the spectrum of RCT findings but may be achievable in general practice when the proper expectations are set and supports are in place.

Admittedly, my evaluation of this teaching tool is anecdotal, derived from my experience and others who I have been able to influence to use it likewise. However, I have found that for patients unaccustomed to treatment with antidepressants, the effect of the message conveyed by the illustration along with a complementary verbal discussion can have a profound effect on their comfort and willingness at the start of treatment. It has also been effective in educating family members about the role of antidepressant treatment, leading to a therapeutic alliance that goes beyond the patient.

In their systematic review of medication compliance in chronic diseases, Haynes et al noted that current methods of improving adherence are mostly complex and not very effective. (10) The illustration described here is simple, efficient and promotes the development of a therapeutic alliance.

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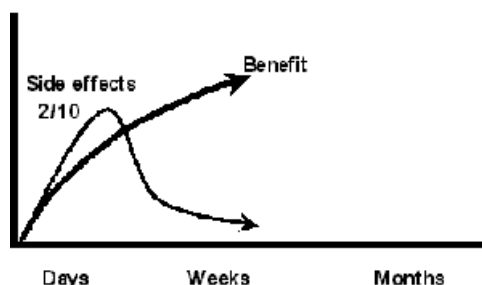
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Panel 1:



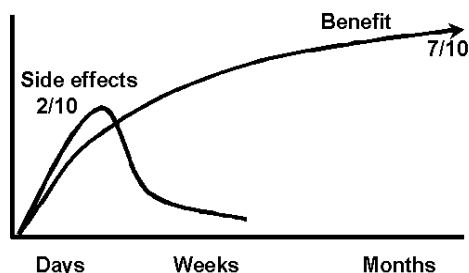
Early in treatment, side effects can occur and can predominate over perceived benefits. However, for most people (~8/10) the side effects are tolerable and resolve within the first few days or weeks of treatment. Some individuals (~2/10) do stop treatment because of side effects early in therapy.

Panel 2:



For many, the benefits of antidepressant therapy are not appreciated until several weeks of treatment have passed. Most individuals notice that they are beginning to feel better at around 4 weeks but continue to improve with therapy well beyond that time.

Panel 3:

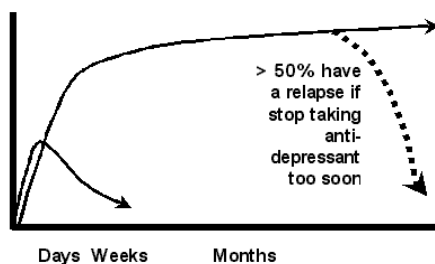


Nearing 8 weeks, approximately 7 people out of 10 who start therapy with an antidepressant achieve a good response and approximately 5 will have complete resolution of their symptoms of depression.

Unfortunately, 3 out of 10 people do not achieve the desired benefits from treatment, whether because of side effects or lack of response or a mixture of factors. It is not possible to determine prior to starting therapy who will respond (a 7 in 10 chance) versus who will not respond adequately (3 in 10 chance).

If a good response does not occur there are other effective treatments available.

Panel 4:



Due to the nature of the underlying depressive episode, stopping therapy too early is associated with a return of depressive symptoms in more than 50% of people, even if they have had a very good response to treatment

Once a good response has been achieved, treatment should continue as directed, which is commonly 6 months or more.

Research Abstracts

The Journal of Informed Pharmacotherapy 2001;7:401.

Faculty of Pharmaceutical Sciences, University of British Columbia Alan C. Hayman Summer Student Research Competition 2001

Partial Proceedings from the Faculty of Pharmaceutical Sciences Summer Student Research Program Poster Competition

Abstracts

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Ivana Dojcinovic, Violet G. Yuen, Mary Battell and John H. McNeill

DEVELOPMENT OF WEB-ENABLED CROSS-DISCIPLINARY CASE-BASED PROBLEMS USING THE FACULTY OF

PHARMACEUTICAL SCIENCES WEB-BASED LEARNING CENTRE (WBLC)

Philip Hui and Simon P. Albon

AN EVALUATION OF FACTORS INFLUENCING THE SAFETY AND EFFICACY OF WARFARIN ANTICOAGULATION

Erin Neall, , Stephen Shalansky and Larry Lynd, Faculty of Pharmaceutical Sciences, The University of British Columbia and St. Paul's Hospital

Objective: The purpose of this study was to measure the frequency and patterns of alternative medication use in patients taking warfarin. This study was also designed as a pilot to assess the relative risk of specific alternative medicines on warfarin-related outcomes in this population.

Methods: A cross-sectional survey was completed by 59 subjects taking warfarin for a variety of indications. Patients were interviewed by phone or in person between June 2001 and August 2001. Prescription records and international normalized ratio (INR) results were also reviewed.

Results: The mean age of the participants was 63.29 (+/-14.31) years and their average dose of warfarin was 4.29 (+/-2.06) mg daily. Thirty-six per cent (n=21) of the patients reported using at least one alternative medication at least once weekly in the previous month, which is a similar frequency to that reported in two previous surveys of Canadian cardiovascular patients. Twenty nine per cent (n=17) reported using an alternative medication that could theoretically interact with warfarin. The most commonly used alternative medications included: vitamin E (22.0%), garlic (8.5%), chamomile (6.8%), and ginko biloba (6.8%), all of which can potentially interact with warfarin. None of the patients reported an increase in their use of alternative medications in the month prior to the interview. The reported exposure to other factors that may influence warfarin's anticoagulation effects included: interacting prescription medication use (50.5%), daily use of interacting over-the-counter medications (40.7%), concomitant illness (30.5%), and change in consumption of foods containing Vitamin K (8.5%). Ongoing analysis will assess the relative risk of specific alternative medicines on the incidence of warfarin-related outcomes (bleed or elevated INR). This analysis will control for the influence of other factors, listed above, known to influence warfarin anticoagulation.

Conclusions: Patients taking warfarin commonly report the use of alternative medications that have been reported to increase bleeding risk through various mechanisms. Pharmacists should review the potential implications of alternative medicine use when counseling patients prescribed oral anticoagulants.

Acknowledgements: Funding for this project was provided by the Canadian Institute of Health Research and the St. Paul's Hospital Foundation. We are grateful to Biljana Radulovic for her help recruiting patients for this survey.

EVALUATION OF PHARMACEUTICAL CARE INTERVENTIONS BY SPEP STUDENTS

Anita Sabatino and Rosemin Kassam. Faculty of Pharmaceutical Sciences, University of British Columbia

Objective: To quantify the impact of undergraduate students on the provision of pharmaceutical care for the first year of the Structured Practice Educational Program (SPEP). **Methods:** A descriptive analysis of the processes of care used by undergraduate students during their SPEP rotations was used to quantify their impact on the provision of pharmaceutical care. Community pharmacies meeting the specific SPEP recruitment criteria were recruited as clerkship sites for SPEP. Documentation tools used

to summarize the students' processes of care included the Modified Pharmacist's Work-up of Drug Therapy (PWDT) and the Pharmacy Care plan. The Modified PWDT was completed for all patients who were interviewed by the students. The Pharmacy Care Plan was completed for all interventions (initial and follow-up) made by the students. From the Modified PWDT information was collected regarding the patient's age, gender, medical condition(s), drug therapy, total number of medications, and drug related problems. For each drug-related problem identified, it was noted whether an initial intervention or a followed-up intervention was initiated, and whether the problem had been resolved. From the Pharmacy Care Plans completed, the information collected included the specific drug-related problem category identified, the type of drug-related problem (actual or potential), the medical condition and drug category associated with the drug-related problem, as well as the student's recommendations, actions and outcome of the actions. Information was also recorded when a follow-up assessment was completed, the individual contacted and the outcome of the care being evaluated. Results: Data analysis is currently ongoing. One hundred and twenty two students completed the SPEP clerkship program, with two hundred and fifty community pharmacies participating in the program. Preliminary analysis suggests that students initiated "comprehensive" pharmaceutical care on 96 patients. There were 214 drug-related problems (actual and potential) identified in these patients. The most three most common medical conditions reported by these patients included hypertension, asthma and diabetes. The three most common medications reported included calcium, acetaminophen and metformin. Results of the complete analysis will be presented on September 27, 2001. Conclusions: This study demonstrates that the SPEP program has successfully made the transition from the traditional dispensing-focused clerkship program to one where there is a greater focus on the provision of pharmaceutical care. The results however indicate that the SPEP curriculum needs to emphasize more "comprehensive" pharmaceutical care in the coming years.

DEVELOPMENT OF AN EVALUATION PROFILE FOR THE FACULTY OF PHARMACEUTICAL SCIENCE'S WEB-BASED LEARNING CENTRE

Claire L. Moffett, Simon P. Albon, and Michael D. Pungente. Faculty of Pharmaceutical Sciences, The University of British Columbia.

Purpose: The purpose of this project was to develop an evaluation profile for the Faculty of Pharmaceutical Science's Web-Based Learning Centre (WBLC). The aim of this four-component evaluation profile is to assess the effectiveness and ultimately the sustainability of the WBLC to support student learning and teaching practice within our faculty.

Methods: The initial framework of the evaluation profile was developed based on a literature investigation as well as consultations with external agencies such as Distance Education and Technology (DE&T). An iterative process of design, evaluation, and redesign through a series of intensive brainstorming sessions with the evaluation team and DE&T resulted in the final draft of the profile. A faculty survey for the evaluation process was developed through a series of meetings with the evaluation team. Using the four main components of the evaluation profile, the team focused on the main elements of the evaluation. Further support for the survey development was provided by a primary and secondary literature search. The literary investigation provided guidance regarding the format and wording of the questionnaire.

Results: An evaluation profile containing four components was successfully developed. The evaluation profile was developed to serve as a framework for the future development of specific tools that will be used to evaluate all aspects of the WBLC.

The four main components of the evaluation profile are as follows:

Evaluation Component	Elements
1. Effectiveness of the WBLC	Quality, Usefulness, Patterns of Use and Access
2. Cost/Benefit Analysis	Costs and Benefits
3. Ease of Update	Availability, Flexibility and Time
4. Support	Users and Financial

Conclusions: The evaluation profile of the Faculty of Pharmaceutical Sciences's WBLC was completed. A survey focussing on faculty use and perceptions of the WBLC was completed based on the fourth component of the evaluation profile, and will be implemented in the 2001 - 2002 academic year. This initial evaluation profile will serve as a framework for future development of the WBLC.

Acknowledgements: Funding for this project was provided by the 2001 - 2002 Teaching and Learning Enhancement Fund (TLEF) of the University of British Columbia.

A SURVEY OF PHYSICIAN DISPENSING OF NON-PRESCRIBED EMERGENCY CONTRACEPTIVE PILLS FOR WOMEN IN BRITISH COLUMBIA

Carolyn Cheung, Judith A. Soon, and Marc Levine. Collaboration for Outcomes Research and Evaluation (CORxE UBC), Faculty of Pharmaceutical Sciences, The University of British Columbia.

Purpose: Emergency contraceptive pills (ECPs) are prescribed and distributed in British Columbia through a number of sources, including general practitioners (GPs), emergency departments, public health nurses, Planned Parenthood and university/college student medical services. Historical data on ECP use suggest that only approximately 65% of annual provincial sales of Ovral® can be found in the BC PharmaNet prescription database or in Planned Parenthood and Youth Clinics reports. Thus, the provision of ECPs by physicians without a prescription or "out-of-cupboard" may be as high as 35% of cases. The purpose of the present study was to pilot test a method of surveying GPs in BC to estimate the overall frequency of non-prescribed ECP use in the province and to obtain a sample size estimate for a full study.

Methods: A brief one page questionnaire and cover letter was designed for the GPs survey, and approval was obtained from the UBC Behavioural Research Ethics Board. The protocol involved initial telephone contact with the physician's office to advise that a cover letter and one page questionnaire would be faxed. The physician then completed and faxed the survey to the research group. Telephone contact was made at one week for non-responders. Preliminary evaluation of the survey was conducted with a convenience sample of six Lower Mainland physicians. Based on responses, the survey was modified. Using the BC College of Physician and Surgeons electronic database to filter for GPs, a random sample stratified by health district was prepared of all apparent GPs in the province. A pilot study of 36 GPs from the stratified random sample was conducted. Questionnaires were also designed to assess the distribution of ECPs by public health nurses, emergency departments, and university/college medical

clinics (data not presented).

Results: Based on the data gathered from the preliminary research and ongoing pilot study (n = 14), GPs in BC provide 4.00 ± 4.30 non-prescribed ECP (ECPNON-Rx) treatments and 4.07 ± 5.21 tablets per non-prescribed ECP treatment annually. To date, the pilot study has resulted in a 45% response rate among GPs available to complete the survey. A total of 16.7% of the physicians designated as GPs in the College of Physician and Surgeons database were no longer active.

Conclusions: The findings of this study suggest that "out-of-cupboard" use is projected to be over 63,000 Ovrall® tablets per year. This represents 49% of ECP sales in 2000 previously unaccounted for by PharmaNet, Planned Parenthood and Youth clinic data. Based on combined preliminary research and pilot study data, and assuming a conservative physician response rate of 30%, 237 GPs would have to be sampled to obtain the number of non-prescribed ECP treatments they provide annually ± 1.0 . The full study will be completed within the next six months.

Acknowledgements: Funding for the study was been provided by Women's Health Bureau BC Ministry of Health, BC Women's Hospital and Health Centre, and a CIHR/Burroughs Wellcome Studentship.

INFORMED SHARED DECISION MAKING: AN EXPLORATORY STUDY IN PHARMACY

Maxwell Murray, Simon Albon, Carlyn Volume, William Godolphin, Angela Towle, Lesley Bainbridge, Melinda Suto, and Rosemin Kassam. Faculty of Pharmaceutical Sciences, University of British Columbia, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Faculty of Medicine, University of British Columbia, and School of Rehabilitation Sciences, University of British Columbia.

Background: Through its adoption of the pharmaceutical care (PC) model of practice, the profession of pharmacy is shifting its focus from products to patients. An essential prerequisite to providing PC is the development of a covenantal relationship with the patient. In a covenantal relationship, the pharmacist and patient commit to working as partners in the identification, resolution, and prevention of the patient's drug-related problems. This step of the PC process is essential to ensuring the care provided by the pharmacist centers around the patient's own needs, values, and desires. Building an effective therapeutic relationship requires pharmacists to have highly developed professional and interpersonal skills, specifically those related to communication. These skills, and more specifically, how the relationship is attained, are not well addressed in current pharmacy curricula or continuing education programs. The informed shared decision making (ISDM) model is a model for interpersonal communication originally developed for physicians. This model has the potential to enhance the pharmacist-patient relationship by providing pharmacists with a systematic approach to engaging patients in covenantal relationships. It also provides a mechanism for pharmacists and patients to work collaboratively towards the identification, resolution, and prevention of drug-related problems.

Purpose: The objectives of this study were: 1) to assess the relevance of the physician-developed ISDM competencies to pharmacy practice; 2) to adapt the physician-based ISDM competencies to pharmacy; 3) to identify barriers to implementing ISDM in pharmacy practice; 4) to identify typical situations in which ISDM is or could be used in pharmacy; and 5) to identify potential competencies required by patients to participate in informed shared decision making.

Methods: To meet the objectives of this study, twenty pharmacists, who act as preceptors in the Structured Practice Education Program (SPEP) in the Faculty of Pharmaceutical Sciences at U.B.C., were recruited and interviewed using a standardized interview protocol. Five pharmacists were selected from each of the following categories: hospital pharmacists with BScPharm degrees, hospital pharmacists with PharmD degrees, community pharmacists practicing as dispensing pharmacists, and community pharmacists who practice as disease management consultants. Prior to the interview, each participant received an information package containing a letter outlining the ISDM model, the project objectives,

the list of physician-based ISDM competencies, a sample consent form, and the interview questions. All interviews were conducted face-to-face, tape-recorded, and transcribed verbatim. Demographic data was collected from each pharmacist at the time of the interview. Responses were summarized into tables grouped according to the pharmacist categories. Summaries were analyzed to identify common themes for each category and to produce an overall pharmacist assessment of the physician-based ISDM competencies.

Results: Of the twenty pharmacists interviewed, 55% were males and 45% were females. Twenty-five percent were between the ages of 20 and 29, 35% between 30 and 39, 25% between 40 and 49, and 15% were 50 years of age or older. Nine of the pharmacists had hospital residencies and two had Master's degrees in Pharmaceutical Sciences. The mean time since graduating from their undergraduate pharmacy programs was 14.3 years. For the five pharmacists with PharmD degrees, it has been a mean of 4.8 years since graduating from that program. Results obtained from the interview transcript analysis are currently being summarized.

Conclusions: An analogous set of ISDM competencies can be developed for pharmacists using the competencies already established for physicians using an inductive method of data collection.

Acknowledgements: The authors would like to acknowledge Apotex Inc., The Association of Faculties of Pharmacy of Canada, The College of Pharmacists of British Columbia, The British Columbia Pharmacy Association, and The Faculty of Pharmaceutical Sciences, U.B.C. for their support of this project.

DEVELOPMENT OF A COLLABORATIVE PHARMACIST RESEARCH NETWORK

Stanley Lin, David Fielding, Elan Paluck. CORxE UBC, Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, BC.

Purpose: Growing numbers of practice-based research networks that systemically collect information related to patient care have emerged in most health professions yet large-scale research networks comprised of community pharmacists remain rare. The goal of this study is to develop a community pharmacist research network for the Collaboration for Outcomes Research and Evaluation (CORxE UBC). This project specifically sought to identify facilitators and barriers that are indigenous to pharmacy practice in B.C. for establishing a research network and inform a strategic plan for implementing and maintaining the network.

Methods: Key pharmacy practice stakeholders (n=24) representing independent pharmacies and major pharmacy chains, the BC College of Pharmacists, BC Pharmacy Association, and Continuing Pharmacy Education were invited to attend a focus group meeting. Focus group methodology developed by Kruger (1998) served as the template. In preparation of the focus group, seven open-ended questions tapping various aspects of initiating and maintaining a pharmacist research network were designed, and then subjected to extensive peer and expert review. For the purposes of the study, research was defined as including the tasks of recruiting patients, obtaining informed consent, collecting patient data, and transmitting data to the investigators. During the focus group, large group discussions were audiotaped while small group discussions were recorded by note takers. All findings were later transcribed and systematically analyzed for content and theme.

Results: Participants (n=21) indicated that many pharmacists are interested in research and that initiating a network or recruiting pharmacists to join would not be problematic; however, the endorsement and sanction from management and the university would be critical motivators for their participation. No major difficulties in conducting research within a community pharmacy setting were identified, but the design of study must be simple, clear, applicable to pharmacy practice, and sensitive to pharmacists' needs and workload. Proper training and support for network pharmacists should be provided and reimbursement, either honorary or monetary form, was an important

consideration. Network communications through phone calls, mails, e-mails, and meetings should be regular to meet the needs of the project as well pharmacists. Constant feedback and evaluation of on-going projects would help to maintain interest and morale.

Conclusions: Establishing a Collaborative Pharmacist Research Network appears to be a feasible and acceptable initiative for CORxE UBC. The facilitators and barriers identified and recommendations made with regard to the research network are invaluable in the preparation of CORxE UBC's implementation and maintenance plan for the research network.

Acknowledgements: Funding for this project was provided by CIHR/Burroughs Wellcome Fund.

PATTERNS OF PHYSICIAN PRESCRIBING OF OVRAL® FOR EMERGENCY CONTRACEPTION IN BRITISH COLUMBIA

Howard Chi Sing Lau, Judith Soon, and Marc Levine. Collaboration for Outcomes Research and Evaluation (CORxE UBC). Faculty of Pharmaceutical Sciences. UBC.

Purpose: Unintended pregnancies and subsequent abortions are major public health issues in British Columbia despite evidence that post-coital emergency contraceptive pills (ECPs) are effective. The objectives of this study were to establish baseline data on physician-prescribed ECPs for a prospective evaluation of the expanded access program and to investigate the association between historical trends in the use of physician-prescribed ECPs and pregnancy and abortion rates in BC.

Methods: B.C. PharmaNet prescription records for Ovral® were obtained for the period from January 1, 1996 to December 31, 1999. Prescription records with a quantity of less than 21 tablets were considered to be for possible ECP use. The database records were separated in Excel® by year dispensed, regional health district, and age group. Pregnancy and abortions counts and rates stratified by age group and by health region were obtained from B.C. Vital Statistics for the calendar years 1996-1999.

Results: Between 1996 - 1999, 64.6% of all Ovral® prescriptions were deemed for ECP use. Of those, 94.2% were for a quantity of 4 tablets. The average number of physician-prescribed ECPs during the 4 year period was 10.3 ± 0.4 ECPs/1000 women/year. Though variability was low, there were 5% fewer ECP prescriptions in 1998 and 1999 compared to 1996. There was a regional disparity in the provision of physician-prescribed ECPs, ranging from a low of 3.7/1000 women/year in the Northern Interior health district and a high of 17/1000 women/year in the Richmond health district. During the same 4 year period, there was a trend to declining pregnancy and abortion rates for 15-44 year-olds, by 9.6% and 5.3%, respectively. Among the highest users of ECPs (15 - 24 year olds), the decline in pregnancy and abortion rates could also not be accounted for by the trend in ECP prescribing.

Conclusions: Physician-prescribed Ovral® use for ECPs remained above 10 ECPs/1000 women/year between 1996-1999 and can not account for the observed change in pregnancy and abortion rates. These baseline data will be used to determine whether the December 1, 2000 policy change authorizing pharmacists to be able to initiate ECPs will result in increased access to ECPs by women or are a transfer of ECP prescriptions from physicians to pharmacists.

Acknowledgements: This research was funded in part by the Student Summer Works Program and the David Collins Dawson Fund.

EFFECTIVENESS OF BUPROPION FOR SMOKING CESSATION: A PILOT TEST OF THE BASELINE SURVEY INSTRUMENT

Joanne P. Li, Elan C. Paluck, David W. Fielding. CORxE UBC, Faculty of Pharmaceutical Sciences

Purpose: The purpose of this project is to pilot test a questionnaire that will be used to gather baseline

patient data in a province-wide study investigating the effectiveness of the smoking cessation agent bupropion.

Methods: Previously reported efficacy trials on bupropion were reviewed to observe the baseline characteristics of sample populations measured. Based on these observations, the baseline survey instrument was designed and pre-tested. Peer-, colleague-, and expert-review were employed to establish the instrument's face and content validity. It was then pilot tested for acceptability and readability in a convenience sample of 13 pharmacies over a 5-week period. Participating pharmacists invited smokers 19 years of age or older who were presenting with a prescription for bupropion to complete the questionnaire. Both the pharmacists and patients provided constructive feedback on the clarity of the instrument. Data obtained from completed questionnaires were analyzed with the Statistical Package for Social Sciences (SPSS version 10.0) for Windows.

Results: Recruitment occurred at 9 of the 13 pharmacies, as 4 were unable to recruit participants due to low bupropion use at their pharmacy. A total of 14 bupropion users participated in the pilot test. Of the 14 patients, 50% were female, 71.5% were under the age of 40, and 85.7% rated their health as good or very good compared to others their age. When asked to report their readiness to quit smoking, 21.4% indicated that they plan to quit within the next 6 months, 42.9% within the next month, 28.9% within the next week, and 7.1% had quit successfully for at least one day. Patients scored a mean of 6.27 ($\pm$ 2.70) out of 11 on the Fagerström Tolerance Questionnaire (FTQ), indicating a "high" level of nicotine dependence. Participants reported an average of 2.1 previous attempts at smoking cessation and nicotine gum was the most common method used. 21.4% of participants indicated that they intended to use the nicotine patch as a supplement with to their bupropion therapy.

Conclusions: The questionnaire was well accepted in terms of length, readability, and content by patients and pharmacists. Characteristics of the patient sample in the pilot study were similar to those of participants in the efficacy trials of bupropion. The low number of patients being treated with bupropion in the pilot test region suggests that the sampling strategy for recruiting 450 patients in the full-scale study may need to be reconsidered to obtain the target. Although bupropion therapy is intended to commence one week before the target quit date, 64.3% (n=9) of the patients did not intend to quit within the next week. This suggests that the patients are unaware of this fact, they are not sufficiently motivated to quit smoking, or that they are not planning to initiate the cessation attempt until a later date. Mean FTQ scores were relatively low compared to those of the sample populations of other smoking cessation studies. This, however, may indicate better success with bupropion for this sample of patients since previous research has demonstrated that lower FTQ scores are predictive of bupropion efficacy.

Acknowledgments: CIHR/Burroughs-Wellcome Fund, CORxE UBC Researchers

EFFECTS OF ACETYLSALICYLIC ACID ON DIABETIC HEART DYSFUNCTION

Ivana Dojcinovic, Violet G. Yuen, Mary Battell and John H. McNeill. Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, B.C.

Purpose: One of the most important complications of poorly controlled diabetes is diabetic cardiomyopathy. Patients with diabetic cardiomyopathy have ventricular dysfunction, which can lead to accelerated heart failure. It has been suggested that high doses of acetylsalicylic acid (ASA) can improve the severity of diabetes by lowering plasma glucose concentration. The purpose of this study was to investigate if ASA treatment can improve ventricular heart function in experimental diabetes.

Methods: Male Wistar rats were randomly divided into four groups: control (C), control treated with 50mg/kg ASA (CT), diabetic (D), and diabetic treated with 50mg/kg ASA. Diabetes was induced by a single tail vein injection of streptozotocin (60mg/kg). ASA was administered daily by oral gavage. After

8 weeks of treatment, the hearts were isolated and perfused. Perfusion was initiated in the retrograde manner through the aorta. Cardiac work was initiated by switching from the retrograde mode to the working heart mode so that buffer enters the left ventricle via the left atrium and exits through the aorta. The heart was paced at a constant heart rate of 300 beats/min. Left ventricular performance was assessed in terms of rate of ventricular contraction ($+dP/dT$), rate of ventricular relaxation ($-dP/dT$) and left ventricular developed pressure (LVDP) in response to increasing left atrial filling pressures (preload). The effects of treatment on the food and fluid intake, fasting plasma glucose, triglycerides, free fatty acid and insulin levels were also examined.

Results: Treatment of the control groups with ASA did not produce any changes in food and fluid intake, plasma glucose, triglyceride, free fatty acid, and insulin levels. ASA did not lower the elevated fasting plasma glucose and triglyceride levels in diabetic rat groups. There was also no effect of ASA treatment on the low insulin levels and high food and fluid intake of diabetic rat groups. However, ASA treatment slightly but significantly lowered the free fatty acid levels in diabetic rats. Hearts from both untreated and treated diabetic groups showed a depressed response to increases in atrial filling pressures from 10 to 11 mmHg in terms of $+dP/dT$, $-dP/dT$ and LVDP. The treatment had no effect on the ventricular response in control rats.

Conclusions: ASA did not have any effect on the plasma glucose levels of both control and diabetic rats and was not able to improve ventricular heart function in experimental diabetes under conditions of increasing preload at the dose used in this study.

Acknowledgements: ID was partially funded by Summer Career Placements.

DEVELOPMENT OF WEB-ENABLED CROSS-DISCIPLINARY CASE-BASED PROBLEMS USING THE FACULTY OF PHARMACEUTICAL SCIENCES WEB-BASED LEARNING CENTRE (WBLC)

Philip Hui and Simon P. Albon. Faculty of Pharmaceutical Sciences, The University of British Columbia

Objectives: The objective of this project was to establish an interdisciplinary approach to teaching and learning in the pharmaceutical sciences through the development, implementation and utilization of WBLC-enabled cross-disciplinary case-based problems. Specific aims included: 1) to create an effective and efficient case writing process that addressed student learning needs, faculty learning objectives, course delivery needs and curriculum outcomes; 2) to develop patient-centred, case-based problems that help learners integrate knowledge across the disciplines of pharmaceutical sciences and, 3) to deliver the problems on-line through the WBLC to support the interdisciplinary nature of the cases and to promote fundamental changes to faculty-student contact time.

Methods: Development of cross-disciplinary case-based problems for WBLC delivery required four phases: 1) identifying student learning needs as the foundation for case development; 2) developing cross-disciplinary case-based problems using macro- and micro-processes, 3) implementation planning and 4) web-enabling. Identifying student learning needs involved meeting with faculty members across pharmacy disciplines and with students to determine knowledge and skill sets that were difficult to teach and/or to learn. Knowledge and skills sets were identified with consideration for the WBLC project objectives, course instructional objectives and the ability-based outcomes of the Faculty's new curriculum. Bridging the teaching and learning needs of faculty and students was accomplished using a macro-process to create patient-centered clinical practice topics. The macro-process involved meetings with faculty experts to identify appropriate cross-disciplinary clinical topics and collection of discipline-specific learning materials relevant to the topic. The micro-process, including evaluation, iteration and refinement through faculty interaction, was used to generate the final case and corresponding guiding questions. Implementation planning involved working with faculty members to integrate the case into their course design as an assessable learning opportunity. Web-enabling involved posting the case in the

appropriate WBLC course with strategic linking to appropriate content in the WBLC. Bulletin board forums were set up to facilitate case discussion.

Results: A prototypical WBLC-enabled patient-centred cross-disciplinary case-based problem was successfully created using an effective and efficient case writing process. The case topic involved the use of risperidone in the treatment of schizophrenia. The case was written as a unifying story including five stages of increasing complexity and incorporating aspects of pharmaceuticals and biopharmaceuticals, pharmaceutical chemistry, pharmacology and toxicology, professional practice and clinical pharmacy. The stages can be delivered in a longitudinal fashion to coincide with the progression of learning materials taught at the course and program levels or independently as required. WBLC-enabling provided on-line access to the case and guiding questions along with integration through strategic links to relevant resource materials within the WBLC. Case designer and tutor manuals were developed to support the case. The WBLC-enabled case-based problem will be implemented and tested in Pharmacy 311 during the 2001-2002 academic year.

Conclusions: A prototypical WBLC-enabled patient-centred cross-disciplinary case-based problem was successfully created using an effective and efficient case writing process. This web-enabled case-based problem represents a new pedagogical tool in the Faculty of Pharmaceutical Sciences that is expected to help learners integrate knowledge across the disciplines of pharmaceutical sciences and promote fundamental changes to faculty-student contact time.

Acknowledgements: The authors would like to acknowledge generous support from the University of British Columbia's Teaching and Learning Enhancement Fund (to SPA), the Government of British Columbia's Student Summer Career Placement Program, the Faculty of Pharmaceutical Sciences, Dr. Ric Procyshyn, Dr. Helen Burt, and Ms. Lynda Eccott.

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Pharmacotherapy on the Web

The Journal of Informed Pharmacotherapy 2001;7:500.

Pharmacist's Letter, Ottawa Valley Regional Drug Information Service, HerbMed, National Center for Infectious Diseases Antimicrobial Resistance, Canadian Coordinating Office for Health Technology Assessment

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Pharmacist's Letter, Ottawa Valley Regional Drug Information Service, HerbMed, Herb Research Foundation, National Center for Infectious Diseases Antimicrobial Resistance, Canadian Coordinating Office for Health Technology Assessment

Name of site:	Pharmacist's Letter
Type of site:	Drug therapy /Trends in pharmacy practice
Authoring organization:	Therapeutic Research Centre
Sponsors:	Subscription-based.
Of particular interest to:	Pharmacists
Completeness Score (5)	5
Credibility Score (5)	4.5
Usability Score (5)	4
Why is it useful? (what will it help me DO?):	This site provides concisely summarized excerpts on new developments in drug therapy and trends in pharmacy practice.
Commentary:	The summaries are quite concise with the option to view the full documents from which the summaries are extracted. Information is synthesized from a variety of major journals including JAMA, NEJM, Lancet, Archives of Internal Medicine, etc. Primarily pharmacists as well as physicians write the documents. There is no pharmaceutical industry sponsorship of this site. This is a subscription-based service and members get a monthly newsletter in addition to online access. One year subscription costs US\$85. A good, user friendly site to keep in touch with new developments in drug therapy and pharmacy practice. Well referenced to make it easy to find original articles that summaries are based on.
URL of site:	http://pharmacistsletter.com

Reviewed by: Saira Ebrahim, B.Sc.(Pharm)Name of site: **Ottawa Valley Regional Drug Information Service**

Type of site: Drug information and product availability database.

Authoring organization: Ottawa Regional Valley Regional Drug Information Service & Ottawa Hospital, General Campus Drug Information Service

Sponsors: as above

Of particular interest to: Pharmacotherapy practitioners in Canada

Completeness Score (/5) 4.5

Credibility Score (/5) 4.5

Usability Score (/5) 5

Why is it useful? (what will it help me DO?): Allows users to quickly locate drug information and keeps practitioners up-to-date with the status of newly marketed or recently discontinued health products in Canada.

Commentary: This site provides free access to two up-to-date user-friendly drug databases. The "Drug Information Database" contains indexed material from 24 pharmacy/medical journals and 26 pharmacy newsletters, and provides links to electronic journals when available. The "Product Availability Database" provides practitioners with information on the current status of recently marketed or discontinued products (medications, medical devices, test kits) in Canada. When information is not available in the database, links to Health Canada's Drug Product Database and Notice of Compliance websites have been provided.

The site also has 16 "Pharmacy Related Bookmarks" with a good selection of interesting websites categorized under each. The bookmarks provide quick access to effective resources in areas including Canadian and American pharmacy associations, drug interactions, herbal/natural medicines, and medical specialties.

This site offers bilingual (French and English) service and is maintained by staff drug information pharmacists. There is no sponsorship from pharmaceutical companies, however the site does advertise the sale of its Intravenous Drug Therapy Manual and its Specialty Drug Information Residency position.

URL of site: <http://www.asksam.com/ovrdis>Reviewed by: Karen Tulloch, B.Sc.(Pharm)Name of site: **HerbMed**

Type of site: Herbal database

Authoring organization:	Alternative Medicine Foundation
Sponsors:	Alternative Medicine Foundations, a non-profit organization
Of particular interest to:	Health professionals who deal with patients taking herbal medications.
Completeness Score (/5)	4
Credibility Score (/5)	3
Usability Score (/5)	5
Why is it useful? (what will it help me DO?):	A searchable herbal database which provides information on many herbs such as evidence for activity, contraindications, adverse effects and drug interactions with hyperlinks to the scientific data (from medline) regarding the use of herbs.
Commentary:	The site is simple to navigate. One can search the site or choose from a list of herbs organized by common or scientific name. The site is fast and does not have fancy graphics. Most importantly, readers are able to evaluate the clinical relevance and quality of the studies on herbs themselves. Although the information provided for each herb could be biased, links to the scientific paper from which they extracted the information are provided for verification.
URL of site:	http://www.herbmed.org
Reviewed by:	Christine Davis, B.Sc.(Pharm)

Name of site:	National Center for Infectious Diseases Antimicrobial Resistance
Type of site:	Comprehensive information about antimicrobial resistance issues.
Authoring organization:	U.S. Centers for Disease Control and Prevention, and National Center for Infectious Diseases
Sponsors:	Center for Disease Control
Of particular interest to:	Any health care professional or member of the public interested in information about antimicrobial resistance.
Completeness Score (/5)	4.5
Credibility Score (/5)	4.5
Usability Score (/5)	5
Why is it useful? (what will it help me DO?):	Reviews current general, technical, clinical, and laboratory antimicrobial resistance issues, and provides useful prevention strategies and education tools for health care professionals and patients to help limit the spread of resistance.

Commentary: This is a comprehensive antimicrobial resistance site for both the health care professional and patient. For the health care professional, there is published data on resistance in health care and non health-care sites, full-text clinical guidelines and recommendations for limiting the spread of resistance, organism-specific technical and laboratory fact sheets, scientific publications, and links to other antimicrobial resistance sites. For the public, there is general information such as prevention tips for the spread of resistance, technical fact sheets, and a glossary of resistance terms. This is a very credible, comprehensive, and useable website.

URL of site: <http://www.cdc.gov/drugresistance/index.htm>

Reviewed by: Victoria Cox, B.Sc.(Pharm)

Name of site: **Canadian Coordinating Office for Health Technology Assessment (CCOHTA)**

Type of site: Critical evaluations of health technologies (defined as devices, equipment, procedures or drugs) in Canada.

Authoring organization: CCOHTA

Sponsors: Federal, provincial, and territorial ministries of health in Canada.

Of particular interest to: Pharmacotherapy practitioners, physicians, and health policy-makers.

Completeness Score (/5) 4

Credibility Score (/5) 4.5

Usability Score (/5) 4.5

Why is it useful? (what will it help me DO?): CCOHTA researchers collect, synthesize, and critically evaluate the available information on medical technologies. Efficacy and economic information are considered. Users of the website can peruse this research and make informed decisions about health technologies in Canada.

Commentary: CCOHTA brings a Canadian perspective to health technology assessments. Registration is free, and will allow the user full access to the publications (searchable and available as PDFs or in print format).

URL of site: <http://www.ccohta.ca>

Reviewed by: Elaine Chong, B.Sc.(Pharm)

Name of site: **Herb Research Foundation**

Type of site: Natural product information site

Authoring organization: Herb Research Foundation

Sponsors: Amway, Rexall, Pharmavite, Celestial Seasonings, Traditional Medicinals

Of particular interest to: Patients interested in Natural Products, or Health Care Professionals

Completeness Score (1/5)	2
Credibility Score (1/5)	2
Usability Score (1/5)	4
Why is it useful? (what will it help me DO?):	The site is not very useful to health care professionals.
Commentary:	Although many clinical trials, studies and meta-analysis are cited, the evidence seems to be at best tertiary. Given that most articles lack a reference to an author, it is very difficult to determine their credentials, and therefore the credibility of the information.
URL of site:	http://www.herbs.org
Reviewed by:	D.L. Cecillon. B.Sc.(Pharm)

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Incorrect Text

In the Evidence Based Review article entitled "Effects of Atorvastatin on Early Recurrent Ischemic Events in Acute Coronary Syndromes. Can We Expect a MIRACL from Cholesterol Lowering Therapy?" published in The Journal of Informed Pharmacotherapy 2001;7:204-207, an error occurred on page 205. Under the section "How large was the treatment effect?", the first sentence should read "During the 16-week follow-up period, a primary end point occurred in 14.8% of the atorvastatin group and 17.4% of the placebo group (**p=0.048**), ARR = 2.6% (95% CI 0% to 5.2%), NNT = 38 (95% CI 20 to 11,893)."

[View the Evidence Based Review Article](#)

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Journal of Informed Pharmacotherapy 2000;1 (April-June)

Editorial

- [The Birth of an Online Pharmacotherapy Journal](#)

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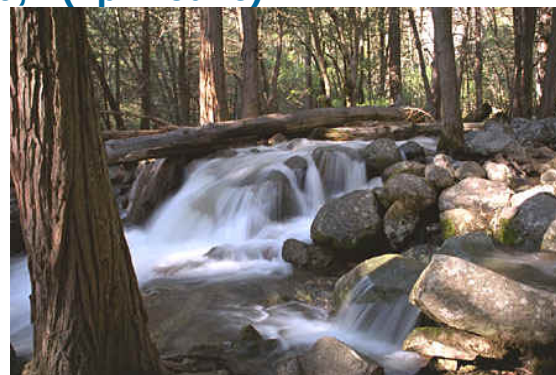
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Editorial

The Birth of an Online Pharmacotherapy Journal

Welcome to the premiere issue of the Journal of Informed Pharmacotherapy, or “the JIP” as we have come to call it. This first issue is the culmination of many months of planning and production on the part of the Editors and we believe it represents a significant advancement in the way scholarly information in the field of pharmacotherapy is disseminated.

The JIP was born in January 1999 as an initiative of the British Columbia Branch of the Canadian Society of Hospital Pharmacists (CSHP). As it developed, both CSHP and the Founding Editors came to realize that the JIP would likely function more effectively as a completely autonomous publication. Despite this, we are indebted to CSHP for its initial support for this project and continue to rely on Canadian pharmacotherapy experts for their editorial assistance and for submissions to the Journal. The JIP receives no funding from the pharmaceutical industry and its operations are supported by an unrestricted educational grant-in-aid from Research Services at Vancouver Hospital & Health Sciences Centre.

Not Just Another Journal

We are well aware of the ongoing proliferation of academic journals in medicine and recognize the increasing difficulty in keeping pace with advances which are relevant to our practices. Despite an increasing number of outlets for authors to disseminate information, we believe that a relatively small proportion of the scholarly work done by many pharmacotherapy researchers and practitioners is ever distributed in a widely disseminated form. Several factors may account for this, not the least of which is the onerous and typically slow traditional peer-review and publication process employed by print-based journals.

The content of the Journal is peer-reviewed by a well recognized panel of Section Editors with expertise in a variety of pharmacotherapeutic specialties. Each section of the JIP is designed to address the challenges faced by busy clinicians and researchers. Specifically, the sections are designed to address the need for widespread and rapid dissemination of peer-reviewed research, for identification and interpretation of important pharmacotherapeutic research using evidence-based principles, for articles on current therapeutic issues written by experts in the field, and for objective reviews of web-based resources designed to enhance clinical practice.

The JIP is not just the online equivalent of a traditional print journal. The online medium and fully electronic processes behind the scenes allows the editorial team of JIP to

accomplish several things which traditional paper-based journals cannot, including:

- Submissions to the Journal for most sections can be accomplished completely online. This eliminates the hassles of paper-based submissions.
- All submissions and subsequent Journal-related communication will be completed using electronic media only to facilitate efficient processing, review and editing.
- Our goal is to achieve a submission to publication interval for accepted manuscripts of two months or less for peer-reviewed original publications and a shorter interval for all other submissions. Compare that to the 6-12 month turnaround time commonly associated with traditional paper-based journals.
- The Journal exists exclusively online, so the costs and distribution delays associated with traditional paper-based journals are avoided.
- Once an article is published, it is instantly available to a worldwide audience.
- Once a paper is published to the website, feedback and critique from other practitioners can occur immediately, and the process of constructive dissection of results can occur in a matter of minutes and hours, rather than months or years as is typical of old-style journals.
- Our low cost of Journal production permits us to maintain this publication without the need for (and potential conflict of interest related to) advertising. This allows us to remain free of private industry support or influence.
- The Journal will be distributed at no cost to the submitting authors or to the readership.

The JIP represents a paradigm shift in scholarly publishing in the field of pharmacotherapy. Much of the rationale for similar journals that now exist in other fields has been eloquently described by the International Consortium for Alternative Academic Publishing and the Scholarly Publishing and Academic Resources Coalition. These groups are at the forefront of overcoming the constraints placed upon researchers, clinicians and university libraries by the soaring costs of for-profit academic journals. These costs have resulted in significant reductions in the number of journals that medical libraries can subscribe to.

Even without this threatening milieu, clinicians require faster access to reliable, up-to-date information that can affect their practice. This is precisely what the JIP seeks to provide.

Of course, ultimately the value of the JIP will be determined by its authors and its readers. We welcome submissions from pharmacotherapy practitioners and researchers on any topic. As with any peer-reviewed journal, your article, if accepted for publication, becomes a permanent part of the medical literature, is locatable with all the major internet search engines, and is fully citable in the Vancouver Group format or using standard web citation format. We also encourage you to respond to the articles you read with criticism, clarification and questions which may help other practitioners. Finally, the Editors welcome your feedback about your needs and suggestions for improvements to the JIP.

We hope that you find the Journal of Informed Pharmacotherapy to be a useful resource and encourage you to check back often for new articles. We urge you to learn more

about the JIP by viewing our [Frequently Asked Questions](#) page, our [information for Authors](#), our [Sponsors page](#), and our [list of Editors](#).

Peter J. Jewesson, BSc(Pharm), PhD, FCSHP

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Carlo A. Marra, BSc(Pharm), PharmD

Peter J. Zed, BSc, BSc(Pharm), PharmD

Publishing Editors

J Inform Pharmacother 2000;1:1.

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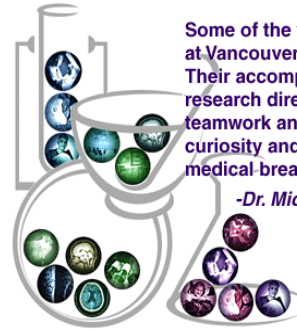
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Some of the world's best medical researchers are at Vancouver Hospital & Health Sciences Centre. Their accomplishments are substantial and their research direction holds great promise. Through teamwork and partnerships, we can sustain the curiosity and provide the support that leads to medical breakthroughs.

-Dr. Michael Smith, 1993 Nobel Prize Winner

The VHHSC Research Strategic Plan

Please direct any inquiries or comments about the Journal to the [Publishing Editors](#). If you have any recommendations for journal content, we would be pleased to receive your ideas.

Last updated: April 19, 2002

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2000;1:200-202.

Does inhibition of the renin-angiotensin-aldosterone system reduce the risk of cardiovascular events? A discussion of HOPE.

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Reviewer: Scot H. Simpson, Pharm.D.

Reviewer's email address: scot.simpson@ualberta.ca

Reviewer's profession/specialty: Research Fellow, EPICORE Centre and Division of Cardiology, University of Alberta

Original Citation

Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. The Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of an angiotensin- converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; 342:145-53. [PubMed Cit](#)

Study Question

The HOPE study was designed to test the theory that inhibition of the renin-angiotensin-aldosterone system would reduce the risk of cardiovascular events. Patients were included in the study if they were 55 years or older, had a history of coronary artery disease, stroke, peripheral vascular disease, or had diabetes plus one or more other cardiovascular risk factors. These patients are considered to be at high risk for cardiovascular events. The primary outcome was a composite endpoint of cardiovascular mortality, myocardial infarction, or stroke.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Patients meeting the inclusion criteria were randomly assigned to one of four treatment groups. The study was a two-by-two factorial design that simultaneously compared the efficacy of ramipril and vitamin E. Randomization was undertaken using a computer-generated sequence and was managed at a central office. Patients were assigned to receive either: 1) ramipril 10 mg and vitamin E 400 IU, 2) ramipril 10 mg and

placebo, 3) placebo and vitamin E 400 IU, or 4) placebo for both ramipril and vitamin E. A sub study compared patients who were randomized to receive 2.5 mg of ramipril, 10 mg of ramipril, or placebo.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. 10,576 patients met the inclusion criteria and entered a run-in phase. All patients received 2.5 mg of ramipril for 7 to 10 days, then placebo for 10 to 14 days. 1035 patients were excluded during the run-in phase due to poor adherence (<80% of pills taken), adverse effects, abnormal serum creatinine or potassium levels, or withdrawal of consent. The remaining patients were randomly assigned to receive ramipril 10 mg (4645 patients), placebo (4652 patients), or ramipril 2.5 mg (244 patients). Vital status was known for 99.9% of the patients at the end of the study. Data were analyzed according to intention-to-treat. The study was terminated early after an independent data and safety monitoring committee found clear evidence of a beneficial effect for ramipril at one of the planned interim analyses.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. Patients and clinicians were blinded to treatment assignment. An expert committee adjudicated all reported endpoints using standardized definitions.

4. Were the groups similar at the start of the trial?

Yes. The baseline characteristics between the ramipril and placebo groups were similar. It is noteworthy that 26.7% were female, 80.4% had a history of coronary artery disease and 38.5% had diabetes.

5. Aside from the experimental intervention, were the groups treated equally?

Yes. All patients were followed in a similar fashion. Follow-up visits occurred at 1 month, then every 6 months. The study was initially planned for a mean of 3.5 years follow-up. However, after a blinded interim analysis revealed a lower than expected event rate, the steering committee decided to extend follow-up to 5 years. Standardized data forms were used to record outcome events, compliance rates and adverse events.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

The primary endpoint for the HOPE trial was a composite of myocardial infarction, stroke, or death from cardiovascular causes. Patients treated with ramipril had a significantly lower risk of reaching the primary endpoint as compared to patients treated with placebo.

Cardiovascular mortality, stroke or myocardial infarction: ramipril = 14.0%; placebo = 17.8%; RRR = 22% (95% CI 14 to 30%), $p < 0.001$; ARR = 3.8%. This translates to an NNT of 26 (95% CI 19 to 40).

Secondary endpoints included each of the individual components of the primary endpoint, all cause mortality, need for revascularization, hospitalization for unstable angina or heart failure, and complications related to diabetes. Treatment with ramipril significantly reduced the risk of each of the secondary endpoints except hospitalization.

There was no information provided regarding the frequency or nature of adverse effects.

2. How precise was the estimate of the treatment effect?

The confidence intervals were relatively narrow, which could be due to the large sample size of the trial. However, treatment with ramipril could reduce the risk of the primary endpoint as much as 5.3% ARR or as “poorly” as 2.5% ARR, which is still considered clinically significant.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. The results of this trial can be applied to a wide range of patients who are at high risk for cardiovascular events. The treatment effect was retained in a number of predefined subgroups controlling for presence of diabetes, gender, presence of cardiovascular disease, age (cut point of 65 years old), presence of hypertension, and presence of microalbuminuria.

2. Were all clinically important outcomes considered?

Yes. Major clinical events were considered, including total and cardiovascular mortality, and various forms of morbidity including hospitalization, need for revascularization, and diabetes-related complications. However, clinically important adverse events, such as renal insufficiency and hypotension were not reported.

3. Are the likely treatment benefits worth the potential harms and

costs?

Yes. The number needed to treat is similar to that for other currently accepted secondary prevention measures such as beta-blockers, acetylsalicylic acid, and lipid-lowering medications. An economic impact of these results is planned.

Commentary

The beneficial effects of angiotensin- converting enzyme inhibitors have been proven in patients with symptomatic and asymptomatic heart failure. With the results of the HOPE trial, use of these agents could be expanded to secondary prevention of cardiovascular events. One finding that warrants further investigation is the reduction in diabetic-related complications, even in patients who do not have diabetes.

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Does inhibition of the renin-angiotensin-aldosterone system reduce the risk of cardiovascular events? A discussion of HOPE.

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Reviewer's profession/specialty: Research Fellow, EPICORE Centre and Division of Cardiology, University of Alberta, Edmonton, Alberta, Canada.

Original Citation

The Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000; 342:145-53.

Overall Study Question

The HOPE study was designed to test the theory that inhibition of the renin-angiotensin-aldosterone system would reduce the risk of cardiovascular events. Patients were included in the study if they were 55 years or older, had a history of coronary artery disease, stroke, peripheral vascular disease, or had diabetes plus one or more other cardiovascular risk factors. These patients are considered to be at high risk for cardiovascular events. The primary outcome was a composite endpoint of cardiovascular mortality, myocardial infarction, or stroke.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Patients meeting the inclusion criteria were randomly assigned to one of four treatment groups. The study was a two-by-two factorial design that simultaneously compared the efficacy of ramipril and vitamin E. Randomization was undertaken using a computer-generated sequence and was managed at a

central office. Patients were assigned to receive either: 1) ramipril 10 mg and vitamin E 400 IU, 2) ramipril 10 mg and placebo, 3) placebo and vitamin E 400 IU, or 4) placebo for both ramipril and vitamin E. A sub study compared patients who were randomized to receive 2.5 mg of ramipril, 10 mg of ramipril, or placebo.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. 10,576 patients met the inclusion criteria and entered a run-in phase. All patients received 2.5 mg of ramipril for 7 to 10 days, then placebo for 10 to 14 days. 1035 patients were excluded during the run-in phase due to poor adherence (<80% of pills taken), adverse effects, abnormal serum creatinine or potassium levels, or withdrawal of consent. The remaining patients were randomly assigned to receive ramipril 10 mg (4645 patients), placebo (4652 patients), or ramipril 2.5 mg (244 patients). Vital status was known for 99.9% of the patients at the end of the study. Data were analyzed according to intention-to-treat. The study was terminated early after an independent data and safety monitoring committee found clear evidence of a beneficial effect for ramipril at one of the planned interim analyses.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

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Yes. Patients and clinicians were blinded to treatment assignment. An expert committee adjudicated all reported endpoints using standardized definitions.

4. Were the groups similar at the start of the trial?

Yes. The baseline characteristics between the ramipril and placebo groups were similar. It is noteworthy that 26.7% were female, 80.4% had a history of coronary artery disease and 38.5% had diabetes.

5. Aside from the experimental intervention, were the groups treated equally?

Yes. All patients were followed in a similar fashion. Follow-up visits occurred at 1 month, then every 6 months. The study was initially planned for a mean of 3.5 years follow-up. However, after a blinded interim analysis revealed a lower than expected event rate, the steering committee decided to extend follow-up to 5 years. Standardized data forms were used to record outcome events, compliance rates and adverse events.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

The primary endpoint for the HOPE trial was a composite of myocardial infarction, stroke, or death from cardiovascular causes. Patients treated with ramipril had a significantly lower risk of reaching the primary endpoint as compared to patients treated with placebo.

Cardiovascular mortality, stroke or myocardial infarction: ramipril = 14.0%; placebo = 17.8%; RRR =

22% (95% CI 14 to 30%), $p < 0.001$; ARR = 3.8%. This translates to an NNT of 26 (95% CI 19 to 40).

Secondary endpoints included each of the individual components of the primary endpoint, all cause mortality, need for revascularization, hospitalization for unstable angina or heart failure, and complications related to diabetes. Treatment with ramipril significantly reduced the risk of each of the secondary endpoints except hospitalization.

There was no information provided regarding the frequency or nature of adverse effects.

2. How precise was the estimate of the treatment effect?

The confidence intervals were relatively narrow, which could be due to the large sample size of the trial. However, treatment with ramipril could reduce the risk of the primary endpoint as much as 5.3% ARR or as “poorly” as 2.5% ARR, which is still considered clinically significant.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. The results of this trial can be applied to a wide range of patients who are at high risk for cardiovascular events. The treatment effect was retained in a number of predefined subgroups controlling for presence of diabetes, gender, presence of cardiovascular disease, age (cut point of 65 years old), presence of hypertension, and presence of microalbuminuria.

2. Were all clinically important outcomes considered?

Yes. Major clinical events were considered, including total and cardiovascular mortality, and various forms

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of morbidity including hospitalization, need for revascularization, and diabetes-related complications. However, clinically important adverse events, such as renal insufficiency and hypotension were not reported.

3. Are the likely treatment benefits worth the potential harms and costs?

Yes. The number needed to treat is similar to that for other currently accepted secondary prevention measures such as beta-blockers, acetylsalicylic acid, and lipid-lowering medications. An economic impact of these results is planned.

Commentary

The beneficial effects of angiotensin-converting enzyme inhibitors have been proven in patients with symptomatic and asymptomatic heart failure. With the results of the HOPE trial, use of these agents could be expanded to secondary prevention of cardiovascular events. One finding that warrants further investigation is the reduction in diabetic-related complications, even in patients who do not have diabetes.

J Inform Pharmacother 2000;1:200-202.

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2000;1:203-204.

A new use for an old drug: Spironolactone for heart failure.

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Reviewer: James McCormack, Pharm.D.

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Reviewer's profession/specialty: Assoc. Professor, Faculty of Pharmaceutical Sciences, University of British Columbia

Original Citation

Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341:709-17. [PubMed Citation](#)

Overall Study Question

The objectives of this trial were to determine the benefit on morbidity and mortality of adding low dose (25-50mg/day) spironolactone to patients with severe heart failure already receiving ACE inhibitors, diuretics and digoxin.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes, patients meeting the inclusion criteria were randomly assigned to receive 25 mg of oral spironolactone (842 patients) or placebo (841 patients) once daily. After 8 weeks the spironolactone dose could be increased to 50 mg if the patient showed signs or symptoms of progressive heart failure. The results of this trial can be applied to a wide range of patients who are at high risk for cardiovascular events.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Unable to determine. Two hundred patients in the placebo group and 214 patients in the spironolactone discontinued treatment reportedly due to lack of response, side effects, or for administrative reasons. Whether all patients were followed up at the conclusion of the study was not reported, although patients who discontinued treatment were followed with regular telephone calls to determine their vital status.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes.

4. Were the groups similar at the start of the trial?

Yes. The baseline characteristics between the spironolactone and placebo groups were similar.

5. Aside from the experimental intervention, were the groups treated equally?

Yes.

6. Overall, are the results of the study valid?

Yes.

What Were the Results?

1. How large was the treatment effect?

The trial was stopped early after a mean of 24 months follow up. Spironolactone reduced hospitalizations due to cardiac causes from 40% to 32%, death from cardiac causes from 37% to 28%, and death from any cause from 46% to 35% (NNT for 48 months were 13, 11 and 9, respectively). In the spironolactone group, patient condition (change in heart failure class) improved for 41% of patients, was unchanged for 21%, and worsened in the remaining 38% of patients. In the placebo group, 33% of patients improved, 18% were unchanged and 48% worsened.

2. How precise was the estimate of the treatment effect?

Unknown. Confidence intervals for the absolute differences were not provided.

Are the Results of the Study Valid?

1.

Can the results be applied to my patient care?

Yes. For patients with Class III or IV heart failure the addition of spironolactone reduces the incidence of 3 clinically important outcomes (i.e. hospitalizations due to cardiac causes, death from cardiac causes, and death from any cause) by a clinically important amount (8-10% absolute difference). In addition, there was a clinically important change in heart failure class for about 10% of patients over the placebo group.

2. Were all clinically important outcomes considered?

Yes. Other than quality of life issues, it appears that all the clinically important outcomes were considered.

3. Are the likely treatment benefits worth the potential harms and costs?

Yes. There were no differences in overall adverse effects between the groups; however, 3% more patients withdrew as a result of adverse events in the spironolactone group. There was a difference in the incidence of gynecomastia (9% spironolactone versus 1% on placebo). There was no difference in the incidence of serious hyperkalemia between the groups. Since spironolactone is available as a generic drug, the cost should not be much of an issue.

Commentary

This study demonstrates that the use of spironolactone can provide a clinically important benefit to patients with Class III and IV heart failure who are already receiving standard therapy (i.e. loop diuretics, ACE inhibitors and digoxin). Given the low incidence of side effects and the low cost of spironolactone, all patients with Class III or IV heart failure should be given a trial of spironolactone. Whether patients with less severe heart failure would benefit is unknown.

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A new use for an old drug: Spironolactone for heart failure.

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Reviewer's profession/specialty: Assoc. Professor, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada

Original Citation

The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341:709-17.

Overall Study Question

The objectives of this trial were to determine the benefit on morbidity and mortality of adding low dose (25-50mg/day) spironolactone to patients with severe heart failure already receiving ACE inhibitors, diuretics and digoxin.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes, Patients meeting the inclusion criteria were randomly assigned to receive 25 mg of oral spironolactone (842 patients) or placebo (841 patients) once daily. After 8 weeks the spironolactone dose could be increased to 50 mg if the patient showed signs or symptoms of progressive heart failure.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Unable to determine. Two hundred patients in the placebo group and 214 patients in the spironolactone discontinued treatment reportedly due to lack of response, side effects, or for administrative reasons. Whether all patients were followed up at the conclusion of the study was not reported, although patients

who discontinued treatment were followed with regular telephone calls to determine their vital status.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes.

4. Were the groups similar at the start of the trial?

Yes. The baseline characteristics between the spironolactone and placebo groups were similar.

5. Aside from the experimental intervention, were the groups treated equally?

Yes.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

The trial was stopped early after a mean of 24 months follow up. Spironolactone reduced hospitalizations due to cardiac causes from 40% to 32%, death from

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cardiac causes from 37% to 28%, and death from any cause from 46% to 35% (NNT for 48 months were 13, 11 and 9, respectively). In the spironolactone group, patient condition (change in heart failure class) improved for 41% of patients, was unchanged for 21%, and worsened in the remaining 38% of patients. In the placebo group, 33% of patients improved, 18% were unchanged and 48% worsened.

2. How precise was the estimate of the treatment effect?

Unknown. Confidence intervals for the absolute differences were not provided.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. For patients with Class III or IV heart failure the addition of spironolactone reduces the incidence of 3 clinically important outcomes (i.e. hospitalizations due to cardiac causes, death from cardiac causes, and death from any cause) by a clinically important amount (8-10% absolute difference). In addition, there was a clinically important change in heart failure class for about 10% of patients over the placebo group.

2. Were all clinically important outcomes considered?

Yes. Other than quality of life issues, it appears that all the clinically important outcomes were considered.

3. Are the likely treatment benefits worth the potential harms and costs?

Yes. There were no differences in overall adverse effects between the groups; however, 3% more patients withdrew as a result of adverse events in the spironolactone group. There was a difference in the incidence of gynecomastia (9% spironolactone versus 1% on placebo). There was no difference in the incidence of serious hyperkalemia between the groups. Since spironolactone is available as a generic drug, the cost should not be much of an issue.

Commentary

This study demonstrates that the use of spironolactone can provide a clinically important benefit to patients with Class III and IV heart failure who are already receiving standard therapy (i.e. loop diuretics, ACE inhibitors and digoxin). Given the low incidence of side effects and the low cost of spironolactone, all patients with Class III or IV heart failure should be given a trial of spironolactone. Whether patients with less severe heart failure would benefit is unknown.

J Inform Pharmacother 2000;1:203-204.

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2000;1:205-207.

The prevention of venous thromboembolism in acutely ill medical patients: Size matters

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Reviewer's profession/specialty: Pharmacy/Internal Medicine

Original Citation

Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, Leizorovicz A, Nguyen H, Olsson CG, Turpie AG, Weisslinger N. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *N Eng J Med* 1999;341:793-800. [PubMed Citation](#)

Overall Study Question

To determine the baseline frequency of venous thromboembolism acutely ill medical patients as well as to determine whether anticoagulation with enoxaparin was effective in reducing the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE).

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes, Patients were randomized to either placebo, 20mg enoxaparin once daily, or 40 mg enoxaparin once daily for 6-14 days during hospitalization.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

All patients were accounted for, although 21.4% of patients randomized were not evaluated (with respect to the primary outcome variable) due to death, patient refusal to submit to

venography, unevaluable venogram, etc. Intention to treat analysis did not include these patients. Such exclusions were evenly balanced between the three groups. 97.4% of patients randomized were included in the safety analysis.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. The study employed a double-blind design.

4. Were the groups similar at the start of the trial?

Yes. The baseline characteristics between the groups were similar.

5. Aside from the experimental intervention, were the groups treated equally?

Yes.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

Venous thromboembolism (detected by leg venography) by day 14 of hospitalization: enoxaparin 40: 5.5% (16/291) ($p < 0.0001$ vs. placebo) enoxaparin 20: 15% (43/287); placebo: 14.9% (43/288). NNT to prevent one asymptomatic DVT (within 15 days of hospitalization) with enoxaparin 40 for 6-14 days vs. placebo = 11. The reduction was significant for both distal or proximal DVT in the 40 mg group vs. placebo. Only 6 of the DVT were symptomatic (spread through the 3 groups). Secondary outcome (DVT reported by patients from discharge to day 110): enoxaparin 40: 7.0% (19/272) ($p < 0.001$) enoxaparin 20: 17.5% (46/263); placebo: 17.1% (45/263). NNT to prevent one symptomatic DVT (during 110 days after hospitalization) with enoxaparin 40 for 6-14 days vs. placebo = 10. Only 4 pulmonary emboli occurred early, 6 occurred late (4 were fatal), thus between group comparisons were not possible. No statistically significant decrease in mortality at 110 days in 40 mg group vs. placebo. There were no significant differences between groups during treatment with respect to thrombocytopenia or major or minor hemorrhage. There were more local injection site reactions in the enoxaparin 40 group than placebo (5 vs. 0; $p = 0.0$).

2. How precise was the estimate of the treatment effect?

The relative risk of DVT within 14 days (enoxaparin 40 vs. placebo) was 0.37 (97.6% CI 0.22-0.63).

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

The benefits of enoxaparin 40 mg therapy may be worth the costs, since other (less expensive) methods of thromboprophylaxis (e.g. unadjusted unfractionated heparin) have not been consistently shown to be effective in this population. The incidence of hemorrhage (major or minor) did not differ significantly between the groups and other adverse effects (e.g.. thrombocytopenia) was non-significantly less common in the enoxaparin 40 mg group than in the placebo arm.

2. Were all clinically important outcomes considered?

Yes. The outcomes measured were relevant and the reporting of outcomes complete.

3. Are the likely treatment benefits worth the potential harms and costs?

Yes. The benefits of enoxaparin 40 mg may be worth the costs, since other (less expensive) methods of thromboprophylaxis (e.g.. unadjusted unfractionated heparin) have not been consistently shown to be effective in this population. The incidence of hemorrhage (major or minor) and other adverse events (e.g. thrombocytopenia) did not differ significantly between the groups.

Commentary

This study is the first large trial to systematically characterize the incidence of proximal and distal DVT among general medical patients. Previous studies have been smaller in size and used less sensitive methods of detection (e.g.. ultrasonography). Although the incidence of asymptomatic DVT was reduced by enoxaparin 40mg in this trial compared to placebo, the occurrence of symptomatic DVT, pulmonary embolism, or post-phlebitic syndrome was too infrequent to conclude that the therapy resulted in an obvious clinical benefit. A much larger trial would be required to establish this. The trend toward a reduction in mortality in this trial, combined with the aggregate data of numerous other DVT prevention trials probably supports the use of the “surrogate” endpoint of venographically detected DVT since the consequences of untreated DVT may be very severe and irreversible. Despite these limitations, this study lends reasonable support to the need to identify patients at risk for DVT in general medicine units and treat them with effective doses of antithrombotic therapy. The evidence to date most strongly supports the administration of enoxaparin 40 mg subcutaneously daily for this indication. Future studies should compare enoxaparin 40 mg daily (or another low molecular weight heparin in comparable doses) to unfractionated heparin in this patient population using the same methodology, since the latter heparin preparation is still widely used despite the lack of reliable data to support its efficacy in preventing DVT in these patients.

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The prevention of venous thromboembolism in acutely ill medical patients: Size matters

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Reviewer's profession/specialty: Pharmacy/Internal Medicine, CSU Pharmaceutical Sciences, Vancouver Hospital and Health Sciences Centre (UBC Hospital Site), Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada

Original Citation

A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. N Eng J Med 1999;341:793-800.

Overall Study Question

To determine the baseline frequency of venous thromboembolism acutely ill medical patients as well as to determine whether anticoagulation with enoxaparin was effective in reducing the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE).

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Patients were randomized to placebo, 20mg enoxaparin once daily, or 40 mg enoxaparin once daily for 6-14 days during hospitalization.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

All patients were accounted for, although 21.4% of patients randomized were not evaluated (with respect to the primary outcome variable) due to death, patient refusal to submit to venography, unevaluable venogram, etc. Intention to treat analysis did not

include these patients. Such exclusions were evenly balanced between the three groups. 97.4% of patients randomized were included in the safety analysis.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. The study employed a double-blind design.

4. Were the groups similar at the start of the trial?

Yes. The baseline characteristics between the groups were similar.

5. Aside from the experimental intervention, were the groups treated equally?

Yes.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

Venous thromboembolism (detected by leg venography) by day 14 of hospitalization: enoxaparin 40: 5.5% (16/291) ($p < 0.0001$ vs. placebo) enoxaparin 20: 15%

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(43/287); placebo: 14.9% (43/288). NNT to prevent one asymptomatic DVT (within 15 days of hospitalization) with enoxaparin 40 for 6-14 days vs. placebo = 11. The reduction was significant for either distal or proximal DVT in the 40 mg group vs. placebo. Only 6 of the DVT were symptomatic (spread through the 3 groups). Secondary outcome (DVT reported by patients from discharge to day 110): enoxaparin 40: 7.0% (19/272) ($p < 0.001$) enoxaparin 20: 17.5% (46/263); placebo: 17.1% (45/263). NNT to prevent one symptomatic DVT (during 110 days after hospitalization) with enoxaparin 40 for 6-14 days vs. placebo = 10. Only 4 pulmonary emboli occurred early, 6 occurred late (4 were fatal), thus between group comparisons were not possible. No statistically significant decrease in mortality at 110 days in 40 mg group vs. placebo. There were no significant differences between groups during treatment with respect to thrombocytopenia or major or minor hemorrhage. There were more local injection site reactions in the enoxaparin 40 group than placebo (5 vs. 0; $p = 0.0$).

2. How precise was the estimate of the treatment effect?

The relative risk of DVT within 14 days (enoxaparin 40 vs. placebo) was 0.37 (97.6% CI 0.22-0.63).

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

The benefits of enoxaparin 40 mg therapy may be worth the costs, since other (less expensive) methods of thromboprophylaxis (e.g. unadjusted unfractionated heparin) have not been consistently shown to be effective in this population. The incidence of hemorrhage (major or minor) did not differ significantly between the groups and other adverse effects (e.g.. thrombocytopenia) was non-significantly less common in the enoxaparin 40 mg group than in the placebo arm.

2. Were all clinically important outcomes considered?

Yes. The outcomes measured were relevant and the reporting of outcomes complete.

3. Are the likely treatment benefits worth the potential harms and costs?

Yes. The benefits of enoxaparin 40 mg may be worth the costs, since other (less expensive) methods of thromboprophylaxis (e.g.. unadjusted unfractionated heparin) have not been consistently shown to be effective in this population. The incidence of hemorrhage (major or minor) and other adverse events (e.g. thrombocytopenia) did not differ significantly between the groups.

Commentary

This study is the first large trial to systematically characterize the incidence of proximal and distal DVT among general medical patients. Previous studies have been smaller in size and used less sensitive methods of detection (e.g.. ultrasonography). Although the incidence of asymptomatic DVT was reduced by enoxaparin 40mg in this trial compared to placebo, the occurrence of symptomatic DVT, pulmonary embolism, or post-phlebotic syndrome was too infrequent to conclude that the therapy resulted in an obvious clinical benefit. A much larger trial would be required to establish this. The trend toward a reduction in mortality in this trial, combined with the aggregate data of numerous other DVT prevention trials probably supports the use of the "surrogate" endpoint of venographically detected DVT since the consequences of untreated DVT may be very severe and irreversible. Despite these limitations, this study lends reasonable support to the need to identify patients at risk for DVT in general medicine units and treat them with effective doses of antithrombotic therapy. The evidence to date most strongly supports the administration of enoxaparin 40 mg subcutaneously daily for this indication. Future studies should compare enoxaparin 40 mg daily (or another low molecular weight heparin in

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comparable doses) to unfractionated heparin in this patient population using the same methodology, since the latter heparin preparation is still widely used despite the lack of reliable data to support its efficacy in preventing DVT in these patients.

J Inform Pharmacother 2000;1:205-207.

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2000;1:208-209.

Infliximab in rheumatoid arthritis: An ATTRACTIVE option?

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Reviewer's email address: cmarra@interchange.ubc.ca

Reviewer's profession/specialty: Pharmacy/Research

Citation

Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, Smolen J, Emery P, Harriman G, Feldmann M, Lipsky P. Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate. ATTRACT Study Group. *Lancet* 1999; 354:1932-1939. [PubMed Citation](#)

Overall Study Question

The ATTRACT study was designed to test whether the addition of infliximab (a chimeric human-mouse anti-TNF α monoclonal antibody) would provide clinical benefit to patients who had active rheumatoid arthritis despite methotrexate treatment. Patients were included in the study if they had active rheumatoid arthritis despite treatment with oral or parenteral methotrexate at a stable dose of at least 12.5 mg/week, and stable doses of corticosteroids (10 mg/kg or less of prednisone) and NSAIDs. The primary outcome was a 20% improvement (according to American College of Rheumatology [ACR] criteria) at the 30 week visit without requiring a surgical joint procedure.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Yes. Eligible patients diagnosed with rheumatoid arthritis with evidence of active disease despite treatment with methotrexate were randomized (in a double-blind fashion) to receive placebo or one of four treatment regimens of infliximab at either 3 mg/kg or 10 mg/kg given every 4 weeks or every 8 weeks and placebo infusions on interim 4 week visits to maintain blinding. All infusions were given over 2 hours.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. 428 patients were enrolled and randomized as follows: 88 to placebo (35 discontinued [d/c'd] prematurely), 86 to 3 mg/kg every 8 weeks (16 d/c'd), 86 to 3mg/kg every 4 weeks (11 d/c'd) , 87 to 10mg/kg every 8 weeks (8 d/c'd) and 81 to 10 mg/kg every 4 weeks. The most common reason for premature discontinuation was inefficacy.

The primary outcome (the ACR defined 20% improvement) was analyzed as intention-to-treat whereas safety was assessed by an on treatment analysis.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. The study was blinded to both the investigators and the patients. The pharmacist at each site held the unblinding code. An evaluator, who had no prior knowledge of other clinical indices and was not involved in the clinical care of the study patient, assessed the joint scores.

4. Were the groups similar at the start of the trial?

Yes. The baseline characteristics of the five treatment groups were well matched in terms of both disease activity (functional class, rheumatoid factor, and duration of disease) and prior to treatment history (previous joint surgery, DMARD exposure and methotrexate dose and duration). Patients in all arms had recalcitrant rheumatoid arthritis of comparable severity.

5. Aside from the experimental intervention, were the groups treated equally?

Yes. All patient groups were reported to have been treated equally. The doses of methotrexate and corticosteroids at baseline were allowed to continue throughout the trial in all arms.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

All groups treated with infliximab had a significantly higher proportion reaching the 20% improvement as specified by the ACR (primary outcome) compared to placebo at 30 months (all $p < 0.001$). The odds ratios (95% CI) were 3.9 (2.0-7.6), 3.9(2.0-7.6), 4.0 (2.1-8.1), and 5.4(2.7-10.6) for the 3 mg/kg every 8 weeks, 3 mg/kg every 4 weeks, 10 mg/kg every 8 weeks, and 10 mg/kg every 4 weeks, respectively. The NNT (and corresponding 95% CI) to generate one additional patient with 20% improvement was 4 (3-8), 4 (3-8), 4(3-7), 3(2-5) for each of the infliximab groups, respectively.

Adverse events between the infliximab arms and the placebo arm were similar. However, the frequency of any infection was significantly higher in those receiving 10 mg/kg every four weeks (73%) vs. placebo (40%). This finding was not significant for the other infliximab regimens and there were no differences between treatment arms for serious (life-threatening or requiring hospitalization) infections. Infusion related reactions occurred in 16-20% of infliximab recipients (depending on treatment arm) compared to 10% of placebo recipients ($p = 0.477$). No delayed hypersensitivity reactions were reported in the trial.

2. How precise was the estimate of the treatment effect?

The 95% CI and corresponding NNT at 30 months are as stated above. It can be seen that none of the CI include zero and thus are statistically significant. In addition, the range of odds ratios represented in the CI are clinically significant.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. The results of this trial can be applied to patients with moderate to severe rheumatoid arthritis who are not currently controlled on methotrexate despite receiving adequate doses. It would appear that anti-tumour necrosis factor agents are an efficacious addition at much lower toxicity than other currently available disease-modifying agents.

2. Were all clinically important outcomes considered?

Yes. The American College of Rheumatology 20% improvement criteria are comprehensive (20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant) measures of disease activity. However, it may have been useful in the trial to have included resource utilization measurements and a generic and disease-specific quality of life measure.

3. Are the likely treatment benefits worth the potential harms and costs?

Yes. Although the numbers needed to treat in this analysis are relatively small compared to other adopted interventions, the cost of this therapy is very high. However, the economic burden associated with severe rheumatoid arthritis is also high thus creating the question "Are the costs of infliximab offset by the downstream avoided costs of rheumatoid arthritis care avoided?" Therefore, a formal economic evaluation should be completed which addresses this question in terms of the benefits and costs in patients treated with infliximab + methotrexate compared to methotrexate alone.

Commentary

Prior to the availability of the results of recent trials of infliximab, methotrexate has been the gold-standard DMARD for use in rheumatoid arthritis. Methotrexate has been traditionally prescribed alone or in combination with other disease modifying drugs. Unfortunately, many patients do not respond or tolerate these agents and thus discontinuation and relapse are common. This trial confirms the added benefit of infliximab in rheumatoid arthritis when added to methotrexate. In addition, it appeared that this agent was well tolerated (although it may cause a dose-related increased risk of infection). Of note, not all patients treated with infliximab + methotrexate responded (proportion of patients reaching the 20% ACR improvement ranged between 50 and 60%). Thus, further research is required into why some patients do not respond to this treatment and further modalities for this group need to be developed.

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Infliximab in rheumatoid arthritis: An ATTRACTIVE option?

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Reviewer's profession/specialty: Pharmacy/Research, CSU Pharmaceutical Sciences, Vancouver Hospital and Health Sciences Centre, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada

Original Citation

Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate. ATTRACT Study Group. *Lancet* 1999; 354:1932-1939.

Overall Study Question

The ATTRACT study was designed to test whether the addition of infliximab (a chimeric human-mouse anti-TNF α monoclonal antibody) would provide clinical benefit to patients who had active rheumatoid arthritis despite methotrexate treatment. Patients were included in the study if they had active rheumatoid arthritis despite treatment with oral or parenteral methotrexate at a stable dose of at least 12.5 mg/week, and stable doses of corticosteroids (10 mg/kg or less of prednisone) and NSAIDs. The primary outcome was a 20% improvement (according to American College of Rheumatology [ACR] criteria) at the 30 week visit without requiring a surgical joint procedure.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes, Eligible patients diagnosed with rheumatoid arthritis with evidence of active disease despite treatment with methotrexate were randomized (in a double-blind fashion) to receive placebo or one of four treatment regimens of infliximab at either 3 mg/kg or

10 mg/kg given every 4 weeks or every 8 weeks and placebo infusions on interim 4 week visits to maintain blinding. All infusions were given over 2 hours.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

428 patients were enrolled and randomized as follows: 88 to placebo (35 discontinued [d/c'd] prematurely), 86 to 3 mg/kg every 8 weeks (16 d/c'd), 86 to 3mg/kg every 4 weeks (11 d/c'd) , 87 to 10mg/kg every 8 weeks (8 d/c'd) and 81 to 10 mg/kg every 4 weeks. The most common reason for premature discontinuation was inefficacy.

The primary outcome (the ACR defined 20% improvement) was analyzed as intention-to-treat whereas safety was assessed by an on treatment analysis.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. The study was blinded to both the investigators and the patients. The pharmacist at each site held the unblinding code. An evaluator, who had no prior knowledge of other clinical indices and was not involved in the clinical care of the study patient, assessed the joint scores.

4. Were the groups similar at the start of the trial?

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Yes. The baseline characteristics of the five treatment groups were well matched in terms of both disease activity (functional class, rheumatoid factor, and duration of disease) and prior to treatment history (previous joint surgery, DMARD exposure and methotrexate dose and duration). Patients in all arms had recalcitrant rheumatoid arthritis of comparable severity.

5. Aside from the experimental intervention, were the groups treated equally?

Yes. All patient groups were reported to have been treated equally. The doses of methotrexate and corticosteroids at baseline were allowed to continue throughout the trial in all arms.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

All groups treated with infliximab had a significantly higher proportion reaching the 20% improvement as specified by the ACR (primary outcome) compared to placebo at 30 months (all $p < 0.001$). The odds ratios (95% CI) were 3.9 (2.0-7.6), 3.9(2.0-7.6), 4.0 (2.1-8.1), and 5.4(2.7-10.6) for the 3 mg/kg every 8 weeks, 3 mg/kg every 4 weeks, 10 mg/kg every 8 weeks, and 10 mg/kg every 4 weeks, respectively. The NNT (and corresponding 95% CI) to generate one additional patient with 20% improvement was 4 (3-8), 4 (3-8), 4(3-7), 3(2-5) for each of the infliximab groups, respectively.

Adverse events between the infliximab arms and the placebo arm were similar. However, the frequency of any infection was significantly higher in those receiving 10 mg/kg every four weeks (73%) vs. placebo (40%). This finding was not significant for the other infliximab regimens and there were no differences between treatment arms for serious (life-threatening or requiring hospitalization) infections. Infusion re-

lated reactions occurred in 16-20% of infliximab recipients (depending on treatment arm) compared to 10% of placebo recipients ($p=0.477$). No delayed hypersensitivity reactions were reported in the trial.

2. How precise was the estimate of the treatment effect?

The 95% CI and corresponding NNT at 30 months are as stated above. It can be seen that none of the CI include zero and thus are statistically significant. In addition, the range of odds ratios represented in the CI are clinically significant.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. The results of this trial can be applied to patients with moderate to severe rheumatoid arthritis who are not currently controlled on methotrexate despite receiving adequate doses. It would appear that anti-tumour necrosis factor agents are an efficacious addition at much lower toxicity than other currently available disease-modifying agents.

2. Were all clinically important outcomes considered?

Yes. The American College of Rheumatology 20% improvement criteria are comprehensive (20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant) measures of disease activity. However, it may have been useful in the trial to include resource utilization measurements and a generic and disease-specific quality of life measure.

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3. Are the likely treatment benefits worth the potential harms and costs?

Yes. Although the numbers needed to treat in this analysis are relatively small compared to other adopted interventions, the cost of this therapy is very high. However, the economic burden associated with severe rheumatoid arthritis is also high thus creating the question "Are the costs of infliximab offset by the downstream avoided costs of rheumatoid arthritis care avoided?" Therefore, a formal economic evaluation should be completed which addresses this question in terms of the benefits and costs in patients treated with infliximab + methotrexate compared to methotrexate alone.

Commentary

Prior to the availability of the results of recent trials of infliximab, methotrexate has been the gold-standard DMARD for use in rheumatoid arthritis. Methotrexate has been traditionally prescribed alone or in combination with other disease modifying drugs. Unfortunately, many patients do not respond or tolerate these agents and thus discontinuation and relapse are common. This trial confirms the added benefit of infliximab in rheumatoid arthritis when added to methotrexate. In addition, it appeared that this agent was well tolerated (although it may cause a dose-related increased risk of infection). Of note, not all patients treated with infliximab + methotrexate responded (proportion of patients reaching the 20% ACR improvement ranged between 50 and 60%). Thus, further research is required into why some patients do not respond to this treatment and further modalities for this group need to be developed.

J Inform Pharmacother 2000;1:208-210.

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2000;1:210-212.

Antimicrobial Therapy in Women with Uncomplicated Pyelonephritis

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Reviewer's profession/specialty: Pharmacy/Emergency Medicine

Original Citation

Talan DA, Stamm WE, Hooton TM, Moran GJ, Burke T, Iravani A, Reuning-Scherer J, Church DA. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women. A randomized trial. *JAMA* 2000;283:1583-90. [PubMed Citation](#)

Overall Study Question

This study was a prospective, multicentre, randomized, double-blind trial designed to compare the safety, efficacy and relative costs of oral ciprofloxacin for 7 days or oral trimethoprim-sulfamethoxazole for 14 days in women with acute uncomplicated pyelonephritis. Premenopausal women at least 18 years of age with a clinical diagnosis of acute uncomplicated pyelonephritis were enrolled in 25 outpatient centers. Eligible patients had flank pain and/or costovertebral angle tenderness; a temperature higher than 38.0C orally, or higher than 38.6C rectally; and pyuria. The primary study endpoints were continued bacteriologic and clinical cure through the 4-11 day posttherapy visit. Secondary endpoints included bacteriologic and clinical responses through the 22-48 day posttherapy visit. Adverse drug events, and health resource use and cost-per-cure analysis from the perspective of the third-party payer were also completed for all enrolled patients.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Initial stratification to decide whether an initial dose of antimicrobial would be given intravenously or orally was made by the treating physician. Patients receiving an initial intravenous dose were administered 400 mg (IV) of ciprofloxacin or 1 g (IV) of

ceftriaxone. Eligible patients were then randomly assigned to receive ciprofloxacin 500 mg or trimethoprim- sulfamethoxazole 160/800 mg tablets (PO) twice daily for 14 days. Ciprofloxacin-treated patients received placebo (PO) twice daily for the final 7 days.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. A total of 378 patients were enrolled and randomized; however, 123 patients were discontinued from the study for reasons including a lack of baseline organisms (40), inadequate administration of study drug (29), patient lost to follow-up (19), inappropriate cultures (15), inadvertent unblinding (4), patient being given another antibiotic for unrelated infection (2) and other protocol violations (14). Thus, 255 patients were considered evaluable for efficacy analysis (128 in the ciprofloxacin group and 127 in the placebo group).

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. Antimicrobial infusions were identical and oral medications were encapsulated in opaque gelatin capsules for blinding purposes.

4. Were the groups similar at the start of the trial?

Yes. Evaluable patients in the treatment groups were well matched with respect to demographic characteristics and symptom severity on study entry.

5. Aside from the experimental intervention, were the groups treated equally?

Yes.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

The primary endpoint of bacteriological cure at 4-11 days posttherapy for efficacy-valid patients was achieved in 99% of ciprofloxacin-treated patients compared to 89% for those treated with trimethoprim-sulfamethoxazole, absolute risk reduction (ARR) 10%, number needed to treat (NNT) 10; (95% confidence interval [CI] 0.04-0.16, $p=0.004$). Clinical cure at 4-11 days posttherapy was achieved in 96% of ciprofloxacin-treated patients compared to 83% for those treated with trimethoprim- sulfamethoxazole, ARR 13%, NNT 8; (95% CI

0.06-0.22, $p=0.002$). These results did not change when evaluated using intention-to-treat analysis for both bacteriologic and clinical cure. Bacteriological cure at the 22-48 days posttherapy was achieved in 85% of ciprofloxacin-treated patients compared to 74% for those treated with trimethoprim-sulfamethoxazole (95% CI 0.00-0.21, $p=0.08$). Clinical cure at 22-48 days posttherapy was achieved in 91% of ciprofloxacin-treated patients compared to 77% for those treated with trimethoprim-sulfamethoxazole, ARR 14%, NNT 8; (95% CI 0.03-0.23, $p=0.02$).

Forty-seven (18.4%) of all uropathogens (44 *E. coli*, 2 *E. aerogenes* and 1 *P. mirabilis*) were resistant to trimethoprim-sulfamethoxazole, while only one strain (*P. mirabilis*) was resistant to ciprofloxacin (0.4%, $p<0.001$). Among trimethoprim-sulfamethoxazole treated patients bacteriological and clinical cure was 50% (7 of 14) and 35% (6 of 17), respectively, as compared to 96% (73 of 76) and 92% (76 of 83) success rates for infections involving susceptible strains.

Adverse effects occurred in 33% of trimethoprim-sulfamethoxazole treated patients compared to 24% for those treated with ciprofloxacin resulting in study discontinuation in 11% and 6%, respectively. Gastrointestinal events (16% vs. 9%), headache (10% vs. 5%) and rash (7% vs. 2%) occurred more frequently in the trimethoprim-sulfamethoxazole group.

Health care resources for hospital stay, return medical visits or telephone consultation, laboratory tests including cultures were all higher in the trimethoprim-sulfamethoxazole-treated patients. The mean total cost per patient was \$687 (US) for the trimethoprim-sulfamethoxazole group and \$531 (US) for the ciprofloxacin group, a difference of \$156 (US) (95% CI -\$118-\$443 (US)). The mean cost per cure was also higher in the trimethoprim-sulfamethoxazole group as compared to ciprofloxacin at \$770 (US) and \$615 (US), a difference of \$155 (95% CI \$102-\$207 (US)).

2. How precise was the estimate of the treatment effect?

The 95% CI for the primary endpoint of continued bacteriologic and clinical cure at days 4-11 did not cross zero indicating statistical significance.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

It would appear that the use of ciprofloxacin 500 mg orally twice daily for 7 days achieves improved bacteriologic and clinical cure compared to trimethoprim-sulfamethoxazole 160-800 mg orally twice daily for 14 days for the treatment of uncomplicated pyelonephritis in women. These results should not be extrapolated to patients with complicated pyelonephritis or those with severe sepsis.

2. Were all clinically important outcomes considered?

Yes. As with any infectious disease-related study, bacteriologic and clinical cure rate and safety assessment are necessary to interpret the impact of each intervention. This was provided. Although not powered to demonstrate a difference between groups, this trial also provided an economic analysis of health resources from the perspective of the third-party payer. This affords clinicians an additional parameter for which to determine the appropriateness of prescribing a more costly agent (i.e. ciprofloxacin) with improved outcomes and the associated reductions in resource consumption that are associated with treatment failures and adverse effects.

3. Are the likely treatment benefits worth the potential harms and costs?

Yes. The improved efficacy of ciprofloxacin was also associated with a reduction in adverse effects and treatment-associated costs.

Commentary

The management of uncomplicated pyelonephritis has not been clearly defined in many clinical trials. In addition, attempts have been made to determine the proper duration of therapy and previous studies suggest that an abbreviated course of therapy may be appropriate. This trial was able to demonstrate that a 7-day course of oral ciprofloxacin was more effective than a 14-day course of trimethoprim-sulfamethoxazole with improved patient tolerance and lower utilization of health resources. Much of the improved benefit of ciprofloxacin could be attributed to the presence of trimethoprim-sulfamethoxazole-resistant strains of E-coli. Although the reason for improved outcome with ciprofloxacin appears obvious, the use of an abbreviated oral regimen with fewer adverse effects and a lower cost is an attractive option in women with uncomplicated pyelonephritis.

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Antimicrobial Therapy in Women with Uncomplicated Pyelonephritis

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Original Citation

Talan DA, Stamm WE, Hooton TM, Moran GJ, Burke T, Iravani A, Reuning-Scherer J, Church DA. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women. A randomized trial. JAMA 2000;283:1583-90.

Overall Study Question

This study was a prospective, multicentre, randomized, double-blind trial designed to compare the safety, efficacy and relative costs of oral ciprofloxacin for 7 days or oral trimethoprim-sulfamethoxazole for 14 days in women with acute uncomplicated pyelonephritis. Premenopausal women at least 18 years of age with a clinical diagnosis of acute uncomplicated pyelonephritis were enrolled in 25 outpatient centers. Eligible patients had flank pain and/or costovertebral angle tenderness; a temperature higher than 38.0°C orally, or higher than 38.6°C rectally; and pyuria. The primary study endpoints were continued bacteriologic and clinical cure through the 4-11 day posttherapy visit. Secondary endpoints included bacteriologic and clinical responses through the 22-48 day posttherapy visit. Adverse drug events, and health resource use and cost-per-cure analysis from the perspective of the third-party payer were also completed for all enrolled patients.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Initial stratification to decide whether an initial dose of antimicrobial would be given intravenously or orally was made by the treating physician. Patients receiving an initial intravenous dose were administered 400 mg (IV) of ciprofloxacin or 1 g (IV) of ceftriaxone. Eligible patients were then randomly assigned to receive ciprofloxacin 500 mg or trimethoprim-sulfamethoxazole 160/800 mg tablets (PO) twice daily for 14 days. Ciprofloxacin-treated patients received placebo (PO) twice daily for the final 7 days.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. A total of 378 patients were enrolled and randomized; however, 123 patients were discontinued from the study for reasons including a lack of baseline organisms (40), inadequate administration of study drug (29), patient lost to follow-up (19), inappropriate cultures (15), inadvertent unblinding (4), patient being given another antibiotic for unrelated infection (2) and other protocol violations (14). Thus, 255 patients were considered evaluable for efficacy analysis (128 in the ciprofloxacin group and 127 in the placebo group).

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

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Yes. Antimicrobial infusions were identical and oral medications were encapsulated in opaque gelatin capsules for blinding purposes.

4. Were the groups similar at the start of the trial?

Yes. Evaluable patients in the treatment groups were well matched with respect to demographic characteristics and symptom severity on study entry.

5. Aside from the experimental intervention, were the groups treated equally?

Yes.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

The primary endpoint of bacteriological cure at 4-11 days posttherapy for efficacy-valid patients was achieved in 99% of ciprofloxacin-treated patients compared to 89% for those treated with trimethoprim-sulfamethoxazole, absolute risk reduction (ARR) 10%, number needed to treat (NNT) 10; (95% confidence interval [CI] 0.04-0.16, $p=0.004$). Clinical cure at 4-11 days posttherapy was achieved in 96% of ciprofloxacin-treated patients compared to 83% for those treated with trimethoprim-sulfamethoxazole, ARR 13%, NNT 8; (95% CI 0.06-0.22, $p=0.002$). These results did not change when evaluated using intention-to-treat analysis for both bacteriologic and clinical cure. Bacteriological cure at the 22-48 days posttherapy was achieved in 85% of ciprofloxacin-treated patients compared to 74% for those treated with trimethoprim-sulfamethoxazole (95% CI 0.00-0.21, $p=0.08$). Clinical

cure at 22-48 days posttherapy was achieved in 91% of ciprofloxacin-treated patients compared to 77% for those treated with trimethoprim-sulfamethoxazole, ARR 14%, NNT 8; (95% CI 0.03-0.23, $p=0.02$).

Forty-seven (18.4%) of all uropathogens (44 *E. coli*, 2 *E. aerogenes* and 1 *P. mirabilis*) were resistant to trimethoprim-sulfamethoxazole, while only one strain (*P. mirabilis*) was resistant to ciprofloxacin (0.4%, $p<0.001$). Among trimethoprim-sulfamethoxazole treated patients bacteriological and clinical cure was 50% (7 of 14) and 35% (6 of 17), respectively, as compared to 96% (73 of 76) and 92% (76 of 83) success rates for infections involving susceptible strains.

Adverse effects occurred in 33% of trimethoprim-sulfamethoxazole treated patients compared to 24% for those treated with ciprofloxacin resulting in study discontinuation in 11% and 6%, respectively. Gastrointestinal events (16% vs. 9%), headache (10% vs. 5%) and rash (7% vs. 2%) occurred more frequently in the trimethoprim-sulfamethoxazole group.

Health care resources for hospital stay, return medical visits or telephone consultation, laboratory tests including cultures were all higher in the trimethoprim-sulfamethoxazole-treated patients. The mean total cost per patient was \$687 (US) for the trimethoprim-sulfamethoxazole group and \$531 (US) for the ciprofloxacin group, a difference of \$156 (US) (95% CI -\$118-\$443 (US)). The mean cost per cure was also higher in the trimethoprim-sulfamethoxazole group as compared to ciprofloxacin at \$770 (US) and \$615 (US), a difference of \$155 (95% CI \$102-\$207 (US)).

2. How precise was the estimate of the treatment effect?

The 95% CI for the primary endpoint of continued bacteriologic and clinical cure at days 4-11 did not cross zero indicating statistical significance.

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Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

It would appear that the use of ciprofloxacin 500 mg orally twice daily for 7 days achieves improved bacteriologic and clinical cure compared to trimethoprim-sulfamethoxazole 160-800 mg orally twice daily for 14 days for the treatment of uncomplicated pyelonephritis in women. These results should not be extrapolated to patients with complicated pyelonephritis or those with severe sepsis.

2. Were all clinically important outcomes considered?

Yes. As with any infectious disease-related study, bacteriologic and clinical cure rate and safety assessment are necessary to interpret the impact of each intervention. This was provided. Although not powered to demonstrate a difference between groups, this trial also provided an economic analysis of health resources from the perspective of the third-party payer. This affords clinicians an additional parameter for which to determine the appropriateness of prescribing a more costly agent (i.e. ciprofloxacin) with improved outcomes and the associated reductions in resource consumption that are associated with treatment failures and adverse effects.

3. Are the likely treatment benefits worth the potential harms and costs?

Yes. The improved efficacy of ciprofloxacin was also associated with a reduction in adverse effects and treatment-associated costs.

Commentary

The management of uncomplicated pyelonephritis has not been clearly defined in many clinical trials. In addition, attempts have been made to determine the proper duration of therapy and previous studies suggest that an abbreviated course of therapy may be appropriate. This trial was able to demonstrate that a 7-day course of oral ciprofloxacin was more effective than a 14-day course of trimethoprim-sulfamethoxazole with improved patient tolerance and lower utilization of health resources. Much of the improved benefit of ciprofloxacin could be attributed to the presence of trimethoprim-sulfamethoxazole-resistant strains of E-coli. Although the reason for improved outcome with ciprofloxacin appears obvious, the use of an abbreviated oral regimen with fewer adverse effects and a lower cost is an attractive option in women with uncomplicated pyelonephritis.

J Inform Pharmacother 2000;1:210-212.

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2000;1:213-215.

Amiodarone for Cardiac ARREST: Implications for Change of Current Practice?

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Reviewer's profession/specialty: Pharmacy/Emergency Medicine

Original Citation

Kudenchuk PJ, Cobb LA, Copass MK, Cummins RO, Doherty AM, Fahrenbruch CE, Hallstrom AP, Murray WA, Olsufka M, Walsh T. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med* 1999;341:871-8. [PubMed Citation](#)

Overall Study Question

ARREST was conducted to determine the efficacy of intravenous amiodarone for the management of shock-refractory ventricular fibrillation or tachycardia in patients with out-of hospital cardiac arrest. Adults with non-traumatic out-of-hospital cardiac arrest were eligible for enrollment if intravenous access had been established and ventricular fibrillation or pulseless ventricular tachycardia (on initial presentation or at any time in the course of resuscitation attempt) was present after three or more precordial shocks had been given. The primary endpoint was admission to hospital with a spontaneous perfusing rhythm. Patients who died in the emergency department were not considered admitted. The secondary endpoints were adverse effects, number of precordial shocks required following the administration of amiodarone or placebo, the total duration of resuscitative measures and the need for additional antiarrhythmic drugs. Survival to discharge from hospital and functional neurological status were also evaluated, although the trial did not have statistical power to demonstrate differences in these outcomes.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. All patients received epinephrine 1 mg intravenously (IV) and were then randomized to received amiodarone 300 mg IV or the diluent, polysorbate 80, as placebo. Only a single dose of amiodarone or placebo was administered.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Of the 667 patients who initially met inclusion criteria, 160 patients did not receive amiodarone or placebo because of spontaneous conversion of their arrhythmia, technical problems or protocol violations. An additional 27 recipients of amiodarone or placebo were determined to be ineligible for the study, but were included in the final analysis. Three eligible patients were excluded from the final analysis, as the treatment assignment was not known due to the loss of an empty study vial. The final study population consisted of 504 patients (246 in the amiodarone group and 258 in the placebo group).

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. Amiodarone and placebo were packaged identically in unlabelled, amber-colored 6 ml glass vials. Each vial was labeled with an identifying number code. Following randomization, the contents of a single vial was drawn into a sterile syringe, diluted to 20 ml with 5% D5W and injected rapidly into a peripheral line that was simultaneously being rapidly infused with 5% D5W. Cardiopulmonary resuscitation was continued during this process. All data were collected and analyzed by investigators who had no knowledge of treatment assignments.

4. Were the groups similar at the start of the trial?

Yes. The baseline characteristics of the amiodarone and placebo groups were similar. The only apparent difference appeared in the initiation of bystander cardiopulmonary resuscitation, which was higher in the amiodarone group (68%) compared to the placebo group (59%, p value unknown).

5. Aside from the experimental intervention, were the groups treated equally?

Yes.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

The primary endpoint, survival to hospital admission, occurred in 44% patients treated with amiodarone compared to 34% of patients who received placebo, (odds ratio [OR] 1.5, 95% confidence interval [CI] 1.04-2.1, $p=0.03$). This correlates to an absolute risk reduction (ARR) of 10% and a number needed to treat of 10. The endpoint was based on admission to hospital so the time frame is from the time of arrest to admission.

The secondary endpoint of survival to hospital discharge was not different between the amiodarone and placebo groups treatment groups (13.4% vs. 13.2%, respectively). Only 52% of all patients who survived to hospital discharge were able to resume independent living activities or returned to work. There was no difference between treatment groups.

There were no differences between treatment groups for any of the other secondary endpoints including the number of precordial shocks required after the administration of amiodarone or placebo, the total duration of resuscitative measures and the need for additional antiarrhythmic drugs.

Overall, amiodarone-treated patients experienced more hypotension requiring pressor therapy compared to placebo (59% vs. 48% ($p=0.04$)) and more bradycardia requiring treatment (41% vs. 25% ($p=0.004$), respectively).

2. How precise was the estimate of the treatment effect?

The 95% CI for the primary endpoint of survival to hospital admission do not include zero indicating statistical significance.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. The use of intravenous amiodarone in patients with out-of hospital cardiac arrest due to shock-refractory ventricular fibrillation or tachycardia amiodarone is more effective than placebo in survival to hospital admission.

2. Were all clinically important outcomes considered?

Although the ARREST trial was able to demonstrate a benefit in the surrogate endpoint of survival to hospital admission the trial was underpowered to evaluate the more clinically relevant endpoint of survival to hospital discharge. In addition, the trial was also underpowered to evaluate the functional neurological status upon discharge from hospital.

3. Are the likely treatment benefits worth the potential harms and costs?

Many questions remain unanswered regarding the use of intravenous amiodarone in patients with cardiac arrest

due to shock-refractory ventricular fibrillation or tachycardia. In addition to the increased cost, it would appear that from an adverse effect perspective, hypotension and bradycardia occur in a large proportion of amiodarone-treated patients. Unfortunately, the ARREST trial did not evaluate the use of amiodarone in comparison with first-line antiarrhythmic therapy used in the Advanced Cardiac Life Support (ACLS) guidelines for ventricular fibrillation or pulseless ventricular tachycardia precluding any definitive conclusions on the role of amiodarone.

Commentary

Although lidocaine, bretylium and procainamide are recommended for use in the ACLS treatment guidelines for ventricular fibrillation and pulseless ventricular tachycardia, the evidence supporting the use of antiarrhythmic therapy has not been clearly established in clinical trials. The ARREST trial is an important trial in the continuum of resuscitation research, but falls short in providing any clear recommendations for use in clinical practice. Although survival to hospital admission was found to be improved in amiodarone-treated patients, this surrogate endpoint did not appear to correlate to improved overall survival nor did its use appear to improve functional neurological status in surviving patients. As the study was underpowered to make any firm conclusions on overall survival and functional neurological status, a larger trial will be required to assess the impact of amiodarone on these endpoints. Since this trial was placebo-controlled (as opposed to a comparison to what would be considered current first-line therapy), these results do not clearly elucidate the role of amiodarone in the current ACLS treatment guidelines for ventricular fibrillation or pulseless ventricular tachycardia. Despite the lack of clear evidence supporting the currently recommended antiarrhythmic agents, clinicians should be cautious when considering the use of amiodarone in this setting until ongoing research (e.g. the ALIVE (Amiodarone versus Lidocaine In Ventricular fibrillation Evaluation) trial) is completed and clinical data is available to compare the efficacy of intravenous amiodarone on overall survival in trials with an appropriate antiarrhythmic control group.

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Amiodarone for Cardiac ARREST: Implications for Change of Current Practice?

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Original Citation

Kudenchuk PJ, Cobb LA, Copass MK, Cummins RO, Doherty AM, Fahrenbruch CE, Hallstrom AP, Murray WA, Olsufka M, Walsh T. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med* 1999;341:871-8.

Overall Study Question

ARREST was conducted to determine the efficacy of intravenous amiodarone for the management of shock-refractory ventricular fibrillation or tachycardia in patients with out-of hospital cardiac arrest. Adults with non-traumatic out-of-hospital cardiac arrest were eligible for enrollment if intravenous access had been established and ventricular fibrillation or pulseless ventricular tachycardia (on initial presentation or at any time in the course of resuscitation attempt) was present after three or more precordial shocks had been given. The primary endpoint was admission to hospital with a spontaneous perfusing rhythm. Patients who died in the emergency department were not considered admitted. The secondary endpoints were adverse effects, number of precordial shocks required following the administration of amiodarone or placebo, the total duration of resuscitative measures and the need for additional antiarrhythmic drugs. Survival to discharge from hospital and functional neurological status were also evaluated, although the trial did not have statistical power to demonstrate differences in these outcomes.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. All patients received epinephrine 1 mg intravenously (IV) and were then randomized to received amiodarone 300 mg IV or the diluent, polysorbate 80, as placebo. Only a single dose of amiodarone or placebo was administered.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Of the 667 patients who initially met inclusion criteria, 160 patients did not receive amiodarone or placebo because of spontaneous conversion of their arrhythmia, technical problems or protocol violations. An additional 27 recipients of amiodarone or placebo were determined to be ineligible for the study, but were included in the final analysis. Three eligible patients were excluded from the final analysis, as the treatment assignment was not known due to the loss of an empty study vial. The final study population consisted of 504 patients (246 in the amiodarone group and 258 in the placebo group).

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

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Yes. Amiodarone and placebo were packaged identically in unlabelled, amber-colored 6 ml glass vials. Each vial was labeled with an identifying number code. Following randomization, the contents of a single vial was drawn into a sterile syringe, diluted to 20 ml with 5% D5W and injected rapidly into a peripheral line that was simultaneously being rapidly infused with 5% D5W. Cardiopulmonary resuscitation was continued during this process. All data were collected and analyzed by investigators who had no knowledge of treatment assignments.

4. Were the groups similar at the start of the trial?

Yes. The baseline characteristics of the amiodarone and placebo groups were similar. The only apparent difference appeared in the initiation of bystander cardiopulmonary resuscitation, which was higher in the amiodarone group (68%) compared to the placebo group (59%, *p* value unknown).

5. Aside from the experimental intervention, were the groups treated equally?

Yes. There were no differences in the further treatment of patients assigned to amiodarone or placebo, including the use of subsequent antiarrhythmic agents.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

The primary endpoint, survival to hospital admission, occurred in 44% patients treated with amiodarone compared to 34% of patients who received placebo, (odds ratio [OR] 1.5, 95% confidence interval [CI] 1.04-2.1, *p*=0.03). This correlates to an absolute

risk reduction (ARR) of 10% and a number needed to treat of 10. The endpoint was based on admission to hospital so the time frame is from the time of arrest to admission.

The secondary endpoint of survival to hospital discharge was not different between the amiodarone and placebo groups (13.4% vs. 13.2%, respectively). Only 52% of all patients who survived to hospital discharge were able to resume independent living activities or returned to work. There was no difference between treatment groups.

There were no differences between treatment groups for any of the other secondary endpoints including the number of precordial shocks required after the administration of amiodarone or placebo, the total duration of resuscitative measures and the need for additional antiarrhythmic drugs.

Overall, amiodarone-treated patients experienced more hypotension requiring pressor therapy compared to placebo (59% vs. 48% (*p*=0.04)) and more bradycardia requiring treatment (41% vs. 25% (*p*=0.004), respectively).

2. How precise was the estimate of the treatment effect?

The 95% CI for the primary endpoint of survival to hospital admission do not include zero indicating statistical significance.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. The use of intravenous amiodarone in patients with out-of hospital cardiac arrest due to shock-refractory ventricular fibrillation or tachycardia amiodarone is more effective than placebo in survival to hospital admission.

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2. Were all clinically important outcomes considered?

Although the ARREST trial was able to demonstrate a benefit in the surrogate endpoint of survival to hospital admission the trial was underpowered to evaluate the more clinically relevant endpoint of survival to hospital discharge. In addition, the trial was also underpowered to evaluate the functional neurological status upon discharge from hospital.

3. Are the likely treatment benefits worth the potential harms and costs?

Many questions remain unanswered regarding the use of intravenous amiodarone in patients with cardiac arrest due to shock-refractory ventricular fibrillation or tachycardia. In addition to the increased cost, it would appear that from an adverse effect perspective, hypotension and bradycardia occur in a large proportion of amiodarone-treated patients. Unfortunately, the ARREST trial did not evaluate the use of amiodarone in comparison with first-line antiarrhythmic therapy used in the Advanced Cardiac Life Support (ACLS) guidelines for ventricular fibrillation or pulseless ventricular tachycardia precluding any definitive conclusions on the role of amiodarone.

vival and functional neurological status, a larger trial will be required to assess the impact of amiodarone on these endpoints. Since this trial was placebo-controlled (as opposed to a comparison to what would be considered current first-line therapy), these results do not clearly elucidate the role of amiodarone in the current ACLS treatment guidelines for ventricular fibrillation or pulseless ventricular tachycardia. Despite the lack of clear evidence supporting the currently recommended antiarrhythmic agents, clinicians should be cautious when considering the use of amiodarone in this setting until ongoing research (e.g. the ALIVE (Amiodarone versus Lidocaine In Ventricular fibrillation Evaluation) trial) is completed and clinical data is available to compare the efficacy of intravenous amiodarone on overall survival in trials with an appropriate antiarrhythmic control group.

J Inform Pharmacother 2000;1:213-215.

Commentary

Although lidocaine, bretylium and procainamide are recommended for use in the ACLS treatment guidelines for ventricular fibrillation and pulseless ventricular tachycardia, the evidence supporting the use of antiarrhythmic therapy has not been clearly established in clinical trials. The ARREST trial is an important trial in the continuum of resuscitation research, but falls short in providing any clear recommendations for use in clinical practice. Although survival to hospital admission was found to be improved in amiodarone-treated patients, this surrogate endpoint did not appear to correlate to improved overall survival nor did it's use appear to improve functional neurological status in surviving patients. As the study was underpowered to make any firm conclusions on overall sur-

Issues in Pharmacotherapy Practice

Breathing Easier: The Role of Leukotriene Modifiers in Chronic Asthma Management

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Abstract

Objective: To review clinical trials evaluating the efficacy of leukotriene modifiers in the treatment of chronic asthma.

Data Source: A MEDLINE search was performed (1966 - March 2000) to identify relevant English-language publications, including preclinical studies, clinical trials, and review articles.

Study Selection and Data Extraction: Controlled-clinical trials of zileuton, zafirlukast, and montelukast in adults and children with asthma were selected to review the efficacy of leukotriene modifiers in asthma management. Information on the safety and efficacy of zileuton, zafirlukast and montelukast, including pharmacokinetic and pharmacologic data are summarized.

Data Synthesis and Results: Leukotrienes elicit many features of asthma such as bronchoconstriction and airway hyperreactivity. In pre-clinical studies, leukotriene modifiers have been shown to attenuate asthmatic responses following various challenges such as exercise, allergen, and acetylsalicylic acid. In placebo-controlled trials, leukotriene modifiers improve pulmonary function, reduce asthma symptoms and short-acting β_2 -agonist use in patients with moderate asthma. The benefits of leukotriene modifiers are generally modest when used as monotherapy, but provide additive benefits when used in conjunction with inhaled corticosteroids. Overall, beclomethasone appears to be superior to montelukast when used in patients with mild-to-moderate asthma while salmeterol appears to be superior to zafirlukast for long-term asthma control. Montelukast may permit a reduction of the required dose of inhaled corticosteroids.

Conclusions: Leukotriene modifiers represent useful adjuncts to inhaled corticosteroids when moderate to high doses of these latter agents are no longer sufficient to control asthma. Leukotriene modifiers may also be considered as first-line monotherapy in patients with mild persistent asthma who choose not to use inhaled corticosteroids.

J Inform Pharmacother 2000;1:300-309.

Introduction

Asthma is a chronic inflammatory disorder of the airways characterized by paroxysmal or persistent symptoms such as dyspnea, chest tightness, wheezing, sputum production and cough associated with

variable airflow obstruction and a variable degree of airway hyperresponsiveness to endogenous or exogenous stimuli (1). Chronic inflammation is now recognized as the key feature in the pathogenesis of asthma and contemporary management strategies are aimed at reducing airway inflammation.

The goals of asthma management, as outlined in the 1999 Canadian Asthma Consensus Report are to: (i) maintain normal or near normal pulmonary function (forced expiratory volume in 1 second; [FEV₁] or peak expiratory flow; [PEF] >85%) with a PEF diurnal variation less than 15%; (ii) reduce the occurrence of daytime asthma symptoms to less than 4 days per week and night-time symptoms to less than 1 night per week; (iii) maintain normal physical activity; (iv) limit exacerbations to mild and infrequent; (v) prevent absenteeism and to; (vi) reduce the need for short-acting β_2 -agonist to a frequency of less than 4 doses per week (1).

To achieve these goals of therapy, medications to treat asthma include the 'relievers' and the 'controllers'. Reliever medications (short-acting β_2 -agonist) are used as needed for prompt relief of asthma symptoms. Controller medications, are generally taken regularly are used to prevent exacerbations. The latter agents include the corticosteroids, leukotriene modifiers, long-acting β_2 -agonist, theophylline and anti-allergic agents (disodium cromoglycate and nedocromil sodium). Inhaled corticosteroids are the mainstay of asthma therapy and should be introduced for patients with moderate asthma symptoms (1).

Leukotriene modifiers were introduced a few years ago for chronic asthma management. Agents currently available are Zileuton (Zyflo®; not available in Canada), Zafirlukast (Accolate®) and Montelukast (Singulair®). Montelukast is approved for use in adults and children 6 years of age or older, zafirlukast in adults and children 7 years of age and older (in the United States) and zileuton in adults only (12 years of age and older). This article reviews leukotriene modifiers, with a focus on their efficacy in controlled clinical trials in the management of chronic asthma.

Leukotriene Biosynthesis and their Role in Asthma

Leukotrienes (LTs) are inflammatory mediators derived from arachidonic acid (AA). In response to various stimuli (e.g. allergen exposure), AA is released from cell-membrane phospholipids by the action of phospholipase A₂ (2,3). Leukotrienes are generated when the enzyme 5-lipoxygenase, and its cofactor 5-lipoxygenase-activating protein metabolizes AA. Arachidonate is initially converted to an unstable intermediate, LTA₄, which is then metabolized by two pathways leading to the formation of LTB₄ or LTC₄. Leukotriene C₄ is actively transported out of cells and rapidly converted to LTD₄ and then to LTE₄. Collectively, LTC₄, LTD₄, and LTE₄ are referred to as the cysteinyl LTs (CysLTs) because of their chemical structure (cysteinyl residues) (2-4). Leukotriene E₄ is mostly recovered in the urine and serves as a marker for LT activity (2).

The CysLTs produce their effect by binding and activating specific receptors. Two subtypes have been identified, CysLT₁ and CysLT₂ receptors (2,5). The CysLT₁ receptor is present on airway cells such as smooth muscle cells and mucus cells. Activation of the CysLT₁ receptor results in smooth muscle constriction; LTC₄ and LTD₄ are equally potent bronchoconstrictors while LTE₄ is only 10% as potent as LTC₄ and LTD₄ (2,3). The CysLT₂ receptor is found in the vascular smooth muscle of the human lung but its function has not been evaluated in humans in vivo (2,5).

Cysteinyl LTs elicit many features of asthma, including contraction of airway smooth muscle, enhanced airway hyperreactivity, increased vascular permeability (leading to airway edema), mucus secretion, and recruitment of neutrophils in the airways (3,4). Zafirlukast and montelukast are selective and specific antagonists of the CysLT₁ receptor (5). In vitro, zafirlukast antagonizes the activity of LTC₄,

LTD₄ and LTE₄. Montelukast inhibits the activity of LTD₄ in receptor-binding studies (6).

Zileuton is a 5-LO inhibitor which binds at or closely to the active site of 5-LO and prevents the metabolism of AA to LTs. The clinical implication of this difference in mechanism of action is unknown (3,6).

Pharmacokinetics of Leukotriene Modifiers

The absolute oral bioavailability of zafirlukast has not been determined (7). However, as mean bioavailability is reduced by about 40% in the presence of food, zafirlukast needs to be taken on an empty stomach (7). Protein binding of zafirlukast is extensive (>99%) mostly to albumin. Zafirlukast is extensively metabolized in the liver, mainly by the cytochrome P450 isoenzyme CYP2C9. Zafirlukast is primarily eliminated in the feces and urinary excretion accounts for less than 10% of an oral dose. The metabolites are less potent than the parent drug and mean terminal half-life of zafirlukast is about 10 hours (7). Zafirlukast is a CYP2C9 and CYP3A4 inhibitor in vitro and thus reduces the metabolism of S-warfarin (more potent isomer) necessitating INR monitoring for those patients on concomitant therapy. Although the clinical impact of these interactions do not seem to be significant, coadministration of theophylline, erythromycin and terfenadine reduce zafirlukast serum concentrations, whereas aspirin increases them (7). Increased serum theophylline concentrations were reported when theophylline was coadministered with zafirlukast (8). Although this drug interaction was not identified when zafirlukast was marketed, careful monitoring is required when these two drugs are used concurrently.

The bioavailability of montelukast is approximately 64% and the drug may be administered with or without food (9). Montelukast is primarily eliminated in the feces as metabolites. The mean terminal half-life of montelukast is between 2.7 to 5.5 hours (9). There appear to be no clinically significant drug interactions with montelukast. Pharmacokinetic studies have failed to demonstrate significant drug interactions with theophylline, warfarin, digoxin, terfenadine, prednisone, prednisolone, and oral contraceptives (10).

Zileuton is well absorbed after oral administration and its bioavailability is not altered by food (10). Zileuton is primarily eliminated as a glucuronide conjugate and a small fraction is metabolized by the CYP2C9, CYP1A2, and CYP3A isoenzymes (10). The metabolites of zileuton are excreted in the feces and urine, and most of the pharmacologic activity is due to the parent drug. The mean terminal half-life of zileuton is 2.5 hours (10). Zileuton reduces the clearance of warfarin and theophylline so INR and theophylline serum concentrations should be closely monitored when these agents are used concurrently with zileuton (10). Zileuton also increases terfenadine serum concentrations and although no cardiac side effects have been reported, most authorities consider it is preferable to avoid concomitant use of these agents (11).

Clinical Trials

Challenge Studies and Dose-Ranging Trials

Challenge studies are usually performed by measuring pulmonary function changes in response to inhalation of a test substance (e.g. histamine) or exercise. Leukotriene modifiers have been compared with placebo in various challenge studies in asthmatics (12-27). Overall, zileuton (12-18), zafirlukast (19-23) and montelukast (24-27) have been shown to attenuate the bronchoconstrictor response to exercise, allergen, aspirin, LTD₄, sulfur dioxide, platelet-activating-factor and exposure to cold/dry air. Results from these trials support the role of LTs in the pathophysiology of asthma and suggest that these agents may be useful in long-term asthma management.

In studies evaluating the effects of various dosages of zafirlukast, most benefits have been achieved with a regimen of 20 mg twice daily (7). Dose-ranging trials for montelukast have established 10 mg/day at bedtime as the optimal dose of the drug in adults, while 5 mg/day at bedtime has been identified as the appropriate dose for children (9). Placebo-controlled trials evaluating two different doses of zileuton demonstrate that 600 mg four times daily provides better asthma control than 400 mg four times daily (28-30). The manufacturer of zileuton recommends using a total daily dose of 2.4 g.

Placebo-Controlled Clinical Trials

The efficacy of zafirlukast 20 mg twice daily over 13 weeks was evaluated in a placebo-controlled trial in 762 adult patients with mild-to-moderate asthma (FEV_1 >55% predicted (mean 79%); mean β_2 -agonist use 4 puffs/day) (31). Zafirlukast increased FEV_1 by 6.3% (difference of 3.3% vs. placebo; $p<0.05$) and improved patient reported endpoints (daytime asthma symptoms, nighttime awakenings, β_2 -agonist use ($p<0.05$) (Table 1). Patients on zafirlukast reduced their use of β_2 -agonist by about 1 puff/day and had fewer asthma exacerbations (difference of 3.8% vs. placebo; $p<0.05$).

A 12-week placebo-controlled trial of Montelukast 10 mg once daily was conducted in 681 adult asthmatics with mild-to-moderate asthma (FEV_1 50-85%, mean 68%; mean β_2 -agonist use 5.4 puffs/day) (32). Twenty-three percent of asthmatics were receiving inhaled corticosteroids. Montelukast improved pulmonary function (increase of 8.9% in FEV_1 vs. placebo; $p<0.001$) and asthma symptoms (Table 1). Use of β_2 -agonist was reduced by about 1 puff/day with montelukast. No significant difference in oral corticosteroid rescue was found between the groups and concomitant use of inhaled corticosteroid did not influence the response to treatment with montelukast. Near-maximal effects on β_2 -agonist use, daytime asthma symptoms and morning PEF were achieved within one day of treatment with montelukast.

The efficacy of montelukast 5 mg once daily was evaluated over 8 weeks in 336 children 6 to 14 years of age with mild-to-moderate asthma (FEV_1 50-85%, mean 72%; average of 3.3 doses/day of short-acting β_2 -agonist) (33). Thirty-nine percent of patients on montelukast and 33% of children on placebo were receiving inhaled corticosteroids. Montelukast provided modest improvements in FEV_1 (difference of 4.65% vs. placebo; $p<0.001$ (Table 1). Use of β_2 -agonist was reduced by less than 1 puff/day ($p=0.08$). Most patient-reported endpoints were similar in subjects on montelukast and placebo at the end of the study. The effects of montelukast on FEV_1 and β_2 -agonist use were similar between patients receiving or not receiving concomitant treatment with inhaled corticosteroids.

Zileuton was studied in 122 adult asthmatics with a mean FEV_1 of 63% predicted and using an average of 5.8 puffs/day of short-acting β_2 -agonist at baseline (29). The FEV_1 increased after the first doses of zileuton and remained improved over the 6-month study period (Table 1). Subjects receiving zileuton had fewer asthma symptoms, lower requirements for short-acting β_2 -agonist or corticosteroids rescue, and fewer asthma exacerbations.

Table 1: Summary of Placebo-Controlled Clinical Trials

Outcome*	Zafirlukast (31)	Montelukast (32,33)	Zileuton (29)
FEV_1	3.3% ($p<0.05$)	adults: 8.9% ($p<0.01$) children: 4.7% ($p<0.01$)	8% ($p=0.004$)

Daytime Asthma Symptoms	13.2% (p>0.01)	adults: decrease (p=NR) children: no difference	decrease (p<0.05)
Nocturnal Asthma Symptoms	-0.47 nights/week (p<0.05)	adults: -0.87 nights/week (p=NR) children: no difference	decrease (p<0.05)
β_2-agonist Use	0.77 puffs/day	adults: decrease (p=NR) children: no difference	1.1 puffs/day (p<0.01)
Corticosteroid Rescue	NR	adults: no difference children: no difference	13.3% (p<0.001)
Asthma Exacerbations	3.8% (p<0.05)	adults: 31% fewer days with worsening symptoms (p<0.001) children: 5.1% less days with worsening asthma symptoms (p=0.049)	11% (p=0.043)

***difference vs. placebo**

NR = not reported, FEV₁ = forced expiratory volume in one second

Overall, LT modifiers have been demonstrated to improve asthma control with improved pulmonary function tests and reduction of symptoms in patients with mild-to-moderate disease who are receiving short-acting β_2 -agonist only. However, the clinical benefits of LT modifiers achieved in placebo-controlled trials are generally modest and monotherapy with these agents is most likely insufficient to achieve the goals of asthma care in patients with moderate or severe asthma.

Comparative Clinical Trials.

The effects of montelukast 10 mg once daily, placebo, and beclomethasone 200 mcg twice daily were evaluated over 12 weeks in 895 patients with moderate asthma (FEV₁ 50-85%, mean 66%, mean short-acting β_2 -agonist use 5.5 puffs/day) (34). Patient response to montelukast or beclomethasone was superior to placebo and the effect of beclomethasone was superior to montelukast. Mean response differences between beclomethasone and montelukast were 5.8% for FEV₁, -0.67 puffs/day for β_2 -agonist use, and -0.7 nights/week for nocturnal awakenings favoring beclomethasone. Montelukast had a faster onset of action (within one day); however, the effects of beclomethasone surpassed that of montelukast after 7 to 10 days of therapy. The incidence of adverse effects was reported to be similar in the three treatment groups. In a 3-week washout period at the end of the study, there was no apparent rebound worsening of asthma symptoms and FEV₁ values returned to baseline in patients receiving montelukast or beclomethasone who were switched to placebo.

Using an intention-to-treat study design, the steroid-sparing effect of montelukast 10 mg once daily was evaluated in 226 asthmatics aged 17-70 years with an FEV₁ >70% (mean 84%) requiring moderate to high doses of inhaled corticosteroids (300-3000 mcg daily) (35). Dosages of inhaled corticosteroids were tapered over 6 weeks before entering a 12-week period of double-blind treatment. Inhaled corticosteroid dose was adjusted every two weeks according to a composite clinical score. Twenty-one

percent of patients (48/226 patients enrolled) did not complete the 12-week period. Montelukast therapy was associated with a reduction in the mean inhaled corticosteroid dose from 976 mcg/day to 526 mcg/day (47% absolute reduction) compared with placebo (from 1079 mcg/day to 727 mcg/day; 30% absolute reduction), without significant changes in FEV₁, asthma symptoms, and β_2 -agonist use. Those patients receiving montelukast had fewer failed rescue episodes (16% vs. 30% with placebo; $p=0.01$). Failed rescue episodes were defined as the number of patients who failed to regain clinical stability after an increase in dose of corticosteroids. This study suggests that montelukast may have a steroid-sparing effect, although the absolute difference in the reduction of corticosteroid dose at the end of 12 weeks appeared to be small (absolute difference of 98 mcg/day or 17.6%; 95% CI: 0.3 to 34.8%; $p=0.046$). Considering the wide 95% CI and the proximity of the lower limit to zero, it is difficult to establish a clinically relevant difference compared to placebo. Differences in potencies between various inhaled corticosteroids was not taken into account when comparing the percentage change in the corticosteroid dose. Finally, the number of patients on different types of inhaled corticosteroids was not reported and equivalent doses were not calculated when comparing groups.

A clinical trial examined the use of montelukast 10 mg once daily in combination with beclomethasone 200 mcg twice daily to determine whether concomitant therapy would yield additional clinical benefits in patients with incompletely controlled asthma (36). Overall, 193 patients were randomly allocated to the montelukast plus beclomethasone group and 200 patients were assigned to the beclomethasone group (placebo tablets once daily and inhaled beclomethasone 200 mcg twice daily). At baseline, patients in both groups had a mean FEV₁ of 71.5% and reported to use about 3.5 puffs/day of short-acting β_2 -agonist. Primary endpoints that were measured in the study were FEV₁ and patient-reported daytime asthma symptoms. The addition of montelukast resulted in improvements in FEV₁ (5.08% vs. 0.72% in the montelukast plus beclomethasone and beclomethasone only groups, respectively, $p<0.001$), daytime asthma symptom scores (-0.13 vs. -0.02, respectively, $p=0.041$) and nocturnal awakenings (-1.04 vs. -0.45, respectively, $p=0.010$); however, total β_2 -agonist use was similar in both groups (-5.51% change from baseline vs. 6.04; $p=0.08$). Montelukast provided additional clinical benefits; however, inclusion of a group on a higher dose of inhaled corticosteroids would have been of interest to determine whether the addition of montelukast is comparable in efficacy to increased doses of corticosteroids.

The efficacy of zileuton was compared with theophylline (target trough serum concentration between 8-15 mcg/ml) in 377 adult asthmatics (mean FEV₁ about 60% predicted) using approximately 6.5 doses of β_2 -agonist daily (37). After 13 weeks of treatment, FEV₁ measurements were similar in patients receiving zileuton and theophylline (increase from baseline of 30.2% vs. 33.7% with zileuton 2.4 g/day and theophylline, respectively). Improvement in morning and evening peak flow measurements, β_2 -agonist requirements (decrease of 1.5 puffs/day vs. 2 puffs/day with zileuton 2.4 g/day and theophylline, respectively), use of rescue corticosteroids, symptom and quality of life scores were not different in subjects on theophylline and zileuton. Overall, the efficacy of zileuton and theophylline was similar in patients with mild-to-moderate asthma.

The efficacy of salmeterol 42 mcg twice daily and zafirlukast 20 mg twice daily was compared over a 4-week period, in a 189 adults with persistent asthma (FEV₁ 50-80%, mean 68%) (38). Approximately 80% of patients in each treatment group were receiving a stable regimen of inhaled corticosteroid at the time of study enrolment. Overall, salmeterol provided greater improvements in pulmonary function and symptom control. Salmeterol increased morning peak flow (primary endpoint) by 29.6 L/min while zafirlukast improved this value by 13.0 L/min. Zafirlukast and salmeterol provided similar improvements in FEV₁, nocturnal awakenings, β_2 -agonist use and asthma exacerbations. The incidence of adverse events was similar in each treatment group. This study was the first published report in which the efficacy of salmeterol and zafirlukast were compared directly. Even though most patients were receiving inhaled corticosteroids, the use of salmeterol is not recommended without concomitant inhaled corticosteroids. Both treatment groups were comparable at baseline, but the dose of inhaled

corticosteroid received during the study was not specified. Finally, this short-term trial is not sufficient to draw conclusions about the efficacy of one agent over the other as an add-on therapy with inhaled corticosteroids. Long-term trials are required to characterize the efficacy of long-acting β_2 -agonist over LT modifiers in chronic asthma management.

Aspirin-Intolerant Asthmatics

The efficacy of zileuton was evaluated in a cross-over study of 40 aspirin-intolerant asthmatics (AIA) (39). Most patients were receiving corticosteroids at baseline. Zileuton improved FEV₁ (difference with placebo after 6 weeks of treatment: 0.19 L; p<0.01), reduced daily β_2 -agonist use (difference with placebo of 0.64 puffs/day; p<0.05), and lowered the scores for loss of smell and rhinorrhea. However, asthma symptoms, peak nasal inspiratory flow rates and nasal congestion scores were similar with zileuton and placebo.

Safety

The incidence of adverse effects is mostly similar in patients receiving LT modifiers and placebo in the clinical trials reviewed. An exception to this is the reversible elevations in liver function tests seen in 2-9% of patients in studies of zileuton (28,29). One patient experienced jaundice, hives, and increased liver function tests which resolved after discontinuation of zileuton (28). Patients on zileuton should have liver function tests performed before starting therapy, every month in the first three months, every 2-3 months for the rest of the first year of treatment, and periodically thereafter (10). Infrequent asymptomatic elevations in serum liver enzymes has been reported with higher than recommended doses of zafirlukast (7).

Concern about the association between Churg-Strauss syndrome and the use of LT modifiers has been raised. Churg-Strauss syndrome is an eosinophilic vasculitis that has been reported in patients with moderate or severe asthma receiving zafirlukast and montelukast. Most patients were undergoing corticosteroid withdrawal after the addition of a LT modifier. It has been postulated that this reaction is not directly related to LT modifiers, but may be an unmasking of the syndrome following corticosteroid withdrawal. A causal relationship between this syndrome and LT modifiers remains unproven and the occurrence of this event is rare (40). Patients with moderate to severe asthma should be monitored for signs and symptoms of the Churg-Strauss syndrome when corticosteroids are tapered or discontinued following the addition of a LT modifier. Leukotriene modifiers are generally well tolerated, but there is limited experience with long-term use of these agents

Discussion

The role of LT modifiers in asthma management is currently being defined. The Expert Panel of the National Asthma Education and Prevention Program states that zafirlukast and zileuton (montelukast was not available at the time of writing of the Expert Panel Report) should be considered as alternative long-term therapies to low-dose inhaled corticosteroids, sodium cromoglycate or nedocromil for patients with mild persistent asthma, but the place of LT modifiers in asthma therapy has not been entirely established (41). The 1999 Canadian Asthma Consensus Report describe the role of LT modifiers as an alternative to low-dose inhaled beclomethasone in patients with mild asthma who cannot tolerate or choose not to use inhaled corticosteroids, although no studies in this population have been published; as an alternative to increased doses of inhaled corticosteroids or as an alternative add-on therapy in place of long-acting β_2 -agonist (1). Unfortunately, few comparative trials are available. To further define their place in therapy, trials comparing LT modifiers with standard therapy, such as inhaled corticosteroids in mild chronic asthma; long-acting bronchodilators in moderate-to-severe asthma; and comparisons to higher doses of inhaled corticosteroids in moderate-to-severe asthma are required. Relevant studies should evaluate primary clinical endpoints that include oral steroid rescue,

unscheduled medical visits, hospitalizations, and asthma exacerbations. These trials are underway and their results may enable clinicians to rank LT modifiers within the armamentarium of asthma therapies.

Leukotriene modifiers differ in terms of frequency of administration, whether they can be taken with food or not, in their safety profile and in their potential for drug interactions. Zileuton is given four times daily, whereas zafirlukast is administered twice daily and montelukast once daily. Zileuton and montelukast may be administered without regards to meals, whereas zafirlukast must be taken on an empty stomach. Zileuton may cause hepatic toxicity and unlike other agents, periodic monitoring of liver function tests is necessary. Zileuton and zafirlukast may influence the elimination and clinical effects of other medications (e.g. warfarin) whereas no drug interactions have been identified with montelukast to date. Finally, whether one agent is superior to another is unknown since no clinical trials have directly compared the efficacy of leukotriene modifiers. Overall, montelukast has many advantages over other agents of this class and may be the LT modifier of choice.

Leukotriene modifiers provide additive benefits to inhaled corticosteroids. In clinical practice, these agents are used in combination with other therapies (i.e. medium or higher doses of inhaled corticosteroids) as an alternative to increasing the corticosteroid dose, or to reduce the corticosteroid dose required to maintain asthma control. Leukotriene modifiers are usually considered as second-line adjunctive therapies to moderate or higher doses of inhaled corticosteroids since more data and clinical experience are available with using long-acting β_2 -agonist. Because they reduce LT-induced airway inflammation, LT modifiers should be the treatment of choice in patients with mild persistent asthma who choose not to use inhaled corticosteroids. Inhaled corticosteroids may prevent the decline in lung function that occurs in patients with asthma, whereas the effect on airway remodeling has not been confirmed with LT modifiers (1). Monotherapy with LT modifiers is insufficient to achieve the goals of asthma therapy in patients with moderate or severe disease.

Clinical trials evaluating montelukast in exercise-induced asthma have demonstrated that it is useful for this indication when used on a regular basis (24,42-45). Leukotriene modifiers are of particular interest in patients with aspirin-induced asthma, which involves a LT-mediated process, but comparative trials remain to be completed. These agents currently have no role for the acute management of asthma exacerbations. Finally, the use of LT modifiers is pregnancy and lactation is not recommended at this time since human data is not available and clinical experience is limited (45).

Leukotriene modifiers have the advantages of being administered orally, of having few side effects and in the case of montelukast, having no drug or food interactions. Unfortunately, asthma control is not improved in all patients receiving LT modifiers. It appears that only 30-50% of patients will respond to therapy, and characteristics which predict response are unknown. Since LT modifiers have a rapid onset of action, a 2-week trial is generally sufficient to determine if patients will benefit from therapy. An exception is when LT modifiers are used in an attempt to reduce the corticosteroid dose, where the trial period is usually longer.

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Breathing Easier: The Role of Leukotriene Modifiers in Chronic Asthma Management

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Objective: To review clinical trials evaluating the efficacy of leukotriene modifiers in the treatment of chronic asthma.

Data Source: A MEDLINE search was performed (1966 - March 2000) to identify relevant English-language publications, including preclinical studies, clinical trials, and review articles.

Study Selection and Data Extraction: Controlled-clinical trials of zileuton, zafirlukast, and montelukast in adults and children with asthma were selected to review the efficacy of leukotriene modifiers in asthma management. Information on the safety and efficacy of zileuton, zafirlukast and montelukast, including pharmacokinetic and pharmacologic data are summarized.

Data Synthesis and Results: Leukotrienes elicit many features of asthma such as bronchoconstriction and airway hyperreactivity. In pre-clinical studies, leukotriene modifiers have been shown to attenuate asthmatic responses following various challenges such as exercise, allergen, and acetylsalicylic acid. In placebo-controlled trials, leukotriene modifiers improve pulmonary function, reduce asthma symptoms and short-acting β_2 -agonist use in patients with moderate asthma. The benefits of leukotriene modifiers are generally modest when used as monotherapy, but provide additive benefits when used in conjunction with inhaled corticosteroids. Overall, beclomethasone appears to be superior to montelukast when used in patients with mild-to-moderate asthma while salmeterol appears to be superior to zafirlukast for long-term asthma control. Montelukast may permit a reduction of the required dose of inhaled corticosteroids.

Conclusions: Leukotriene modifiers represent useful adjuncts to inhaled corticosteroids when moderate to high doses of these latter agents are no longer sufficient to control asthma. Leukotriene modifiers may also be considered as first-line monotherapy in patients with mild persistent asthma who choose not to use inhaled corticosteroids.

J Inform Pharmacother 2000;1:300-309.

Asthma is a chronic inflammatory disorder of the airways characterized by paroxysmal or persistent symptoms such as dyspnea, chest tightness, wheezing, sputum production and cough associated with variable airflow obstruction and a variable degree of airway hyperresponsiveness to endogenous or exogenous stimuli (1). Chronic inflammation is now recognized as the key feature in the pathogenesis of asthma and contemporary management strategies are aimed at reducing airway inflammation.

The goals of asthma management, as outlined in the 1999 Canadian Asthma Consensus Report are to: (i) maintain normal or near normal pulmonary function (forced expiratory volume in 1 second; [FEV₁] or peak expiratory flow; [PEF] >85%) with a PEF diurnal variation less than 15%; (ii) reduce the occurrence of day-time asthma symptoms to less than 4 days per week and night-time symptoms to less than 1 night per week; (iii) maintain normal physical activity; (iv) limit exacerbations to mild and infrequent; (v) prevent absenteeism and to; (vi) reduce the need for short-acting β_2 -agonist to a frequency of less than 4 doses per week (1).

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To achieve these goals of therapy, medications to treat asthma include the 'relievers' and the 'controllers'. Reliever medications (short-acting β_2 -agonist) are used as needed for prompt relief of asthma symptoms. Controller medications, are generally taken regularly are used to prevent exacerbations. The latter agents include the corticosteroids, leukotriene modifiers, long-acting β_2 -agonist, theophylline and anti-allergic agents (disodium cromoglycate and nedocromil sodium). Inhaled corticosteroids are the mainstay of asthma therapy and should be introduced for patients with moderate asthma symptoms (1).

Leukotriene modifiers were introduced a few years ago for chronic asthma management. Agents currently available are Zileuton (Zyflo[®]; not available in Canada), Zafirlukast (Accolate[®]) and Montelukast (Singulair[®]). Montelukast is approved for use in adults and children 6 years of age or older, zafirlukast in adults and children 7 years of age and older (in the United States) and zileuton in adults only (12 years of age and older). This article reviews leukotriene modifiers, with a focus on their efficacy in controlled clinical trials in the management of chronic asthma.

Leukotriene Biosynthesis and their Role in Asthma

Leukotrienes (LTs) are inflammatory mediators derived from arachidonic acid (AA). In response to various stimuli (e.g. allergen exposure), AA is released from cell-membrane phospholipids by the action of phospholipase A2 (2,3). Leukotrienes are generated when the enzyme 5-lipoxygenase, and its cofactor 5-lipoxygenase-activating protein metabolizes AA. Arachidonate is initially converted to an unstable intermediate, LTA₄, which is then metabolized by two pathways leading to the formation of LTB₄ or LTC₄. Leukotriene C₄ is actively transported out of cells and rapidly converted to LTD₄ and then to LTE₄. Collectively, LTC₄, LTD₄, and LTE₄ are referred to as the cysteinyl LTs (CysLTs) because of their chemical structure (cysteinyl residues) (2-4). Leukotriene E₄ is mostly recovered in the urine and serves as a marker for LT activity (2).

The CysLTs produce their effect by binding and activating specific receptors. Two subtypes have been identified, CysLT₁ and CysLT₂ receptors (2,5). The CysLT₁ receptor is present on airway cells such as smooth muscle cells and mucus cells. Activation of the CysLT₁ receptor results in smooth muscle constriction; LTC₄ and LTD₄ are equally potent bronchoconstrictors while LTE₄ is only 10% as potent as LTC₄ and LTD₄ (2,3). The CysLT₂ receptor is found in the vascular smooth muscle of the human lung but its function has not been evaluated in humans in vivo (2,5).

Cysteinyl LTs elicit many features of asthma, including contraction of airway smooth muscle, enhanced airway hyperreactivity, increased vascular permeability (leading to airway edema), mucus secretion, and recruitment of neutrophils in the airways (3,4). Zafirlukast and montelukast are selective and specific antagonists of the CysLT₁ receptor (5). In vitro, zafirlukast antagonizes the activity of LTC₄, LTD₄ and LTE₄. Montelukast inhibits the activity of LTD₄ in receptor-binding studies (6). Zileuton is a 5-LO inhibitor which binds at or closely to the active site of 5-LO and prevents the metabolism of AA to LTs. The clinical implication of this difference in mechanism of action is unknown (3,6).

Pharmacokinetics of Leukotriene Modifiers

The absolute oral bioavailability of zafirlukast has not been determined (7). However, as mean bioavailability is reduced by about 40% in the presence of food, zafirlukast needs to be taken on an empty stomach (7). Protein binding of zafirlukast is extensive (>99%) mostly to albumin. Zafirlukast is extensively metabolized in the liver, mainly by the cytochrome P450 isoenzyme CYP2C9. Zafirlukast is primarily eliminated in the feces and urinary excretion accounts for less than 10% of an oral dose. The metabolites are less potent than the parent drug and mean terminal half-life of zafirlukast is about 10 hours (7). Zafirlukast is a CYP2C9 and CYP3A4 inhibitor in vitro and thus reduces the metabolism of S-warfarin (more potent isomer) necessitating INR monitoring for those patients

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on concomitant therapy. Although the clinical impact of these interactions do not seem to be significant, coadministration of theophylline, erythromycin and terfenadine reduce zafirlukast serum concentrations, whereas aspirin increases them (7). Increased serum theophylline concentrations were reported when theophylline was coadministered with zafirlukast (8). Although this drug interaction was not identified when zafirlukast was marketed, careful monitoring is required when these two drugs are used concurrently.

The bioavailability of montelukast is approximately 64% and the drug may be administered with or without food (9). Montelukast is primarily eliminated in the feces as metabolites. The mean terminal half-life of montelukast is between 2.7 to 5.5 hours (9). There appear to be no clinically significant drug interactions with montelukast. Pharmacokinetic studies have failed to demonstrate significant drug interactions with theophylline, warfarin, digoxin, terfenadine, prednisone, prednisolone, and oral contraceptives (10).

Zileuton is well absorbed after oral administration and its bioavailability is not altered by food.¹⁰ Zileuton is primarily eliminated as a glucuronide conjugate and a small fraction is metabolized by the CYP2C9, CYP1A2, and CYP3A isoenzymes (10). The metabolites of zileuton are excreted in the feces and urine, and most of the pharmacologic activity is due to the parent drug. The mean terminal half-life of zileuton is 2.5 hours (10). Zileuton reduces the clearance of warfarin and theophylline so INR and theophylline serum concentrations should be closely monitored when these agents are used concurrently with zileuton (10). Zileuton also increases terfenadine serum concentrations and although no cardiac side effects have been reported, most authorities consider it is preferable to avoid concomitant use of these agents (11).

Clinical Trials

Challenge Studies and Dose-Ranging Trials

Challenge studies are usually performed by measuring pulmonary function changes in response to inhala-

tion of a test substance (e.g. histamine) or exercise. Leukotriene modifiers have been compared with placebo in various challenge studies in asthmatics (12-27). Overall, zileuton (12-18), zafirlukast (19-23) and montelukast (24-27) have been shown to attenuate the bronchoconstrictor response to exercise, allergen, aspirin, LTD₄, sulfur dioxide, platelet-activating-factor and exposure to cold/dry air. Results from these trials support the role of LTs in the pathophysiology of asthma and suggest that these agents may be useful in long-term asthma management.

In studies evaluating the effects of various dosages of zafirlukast, most benefits have been achieved with a regimen of 20 mg twice daily (7). Dose-ranging trials for montelukast have established 10 mg/day at bedtime as the optimal dose of the drug in adults, while 5 mg/day at bedtime has been identified as the appropriate dose for children (9). Placebo-controlled trials evaluating two different doses of zileuton demonstrate that 600 mg four times daily provides better asthma control than 400 mg four times daily (28-30). The manufacturer of zileuton recommends using a total daily dose of 2.4 g.

Placebo-Controlled Clinical Trials

The efficacy of zafirlukast 20 mg twice daily over 13 weeks was evaluated in a placebo-controlled trial in 762 adult patients with mild-to-moderate asthma (FEV₁ >55% predicted (mean 79%); mean β_2 -agonist use 4 puffs/day) (31). Zafirlukast increased FEV₁ by 6.3% (difference of 3.3% vs. placebo; $p < 0.05$) and improved patient reported endpoints (daytime asthma symptoms, nighttime awakenings, β_2 -agonist use ($p < 0.05$) (Table 1). Patients on zafirlukast reduced their use of β_2 -agonist by about 1 puff/day and had fewer asthma exacerbations (difference of 3.8% vs. placebo; $p < 0.05$).

A 12-week placebo-controlled trial of Montelukast 10 mg once daily was conducted in 681 adult asthmatics with mild-to-moderate asthma (FEV₁ 50-85%, mean 68%; mean β_2 -agonist use 5.4 puffs/day) (32). Twenty-three percent of asthmatics were receiving inhaled corticosteroids. Montelukast improved pulmonary

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Table 1: Summary of Placebo-Controlled Clinical Trials

Outcome*	Zafirlukast (31)	Montelukast (32,33)	Zileuton (29)
FEV ₁	3.3% (p<0.05)	adults: 8.9% (p<0.01) children: 4.7% (p<0.01)	8% (p=0.004)
Daytime Asthma Symptoms	13.2% (p>0.01)	adults: decrease (p=NR) children: no difference	decrease (p<0.05)
Nocturnal Asthma Symptoms	-0.47 nights/week (p<0.05)	adults: -0.87 nights/week (p=NR) children: no difference	decrease (p<0.05)
β ₂ -agonist Use	0.77 puffs/day	adults: decrease (p=NR) children: no difference	1.1 puffs/day (p<0.01)
Corticosteroid Rescue	NR	adults: no difference children: no difference	13.3% (p<0.001)
Asthma Exacerbations	3.8% (p<0.05)	adults: 31% fewer days with worsening symptoms (p<0.001) children: 5.1% less days with worsening asthma symptoms (p=0.049)	11% (p=0.043)

*difference vs. placebo

NR = not reported, FEV₁ = forced expiratory volume in one second

function (increase of 8.9% in FEV₁ vs. placebo; p<0.001) and asthma symptoms (Table 1). Use of β₂-agonist was reduced by about 1 puff/day with montelukast. No significant difference in oral corticosteroid rescue was found between the groups and concomitant use of inhaled corticosteroid did not influence the response to treatment with montelukast. Near-maximal effects on β₂-agonist use, daytime asthma symptoms and morning PEF were achieved within one day of treatment with montelukast. The efficacy of monte-

lukast 5 mg once daily was evaluated over 8 weeks in 336 children 6 to 14 years of age with mild-to-moderate asthma (FEV₁ 50-85%, mean 72%; average of 3.3 doses/day of short-acting β₂-agonist). (33) Thirty-nine percent of patients on montelukast and 33% of children on placebo were receiving inhaled corticosteroids. Montelukast provided modest improvements in FEV₁ (difference of 4.65% vs. placebo; p<0.001 (Table 1). Use of β₂-agonist was reduced by less than 1 puff/day (p=0.08). Most patient-reported endpoints

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were similar in subjects on montelukast and placebo at the end of the study. The effects of montelukast on FEV₁ and β_2 -agonist use were similar between patients receiving concomitant treatment with inhaled corticosteroids.

Zileuton was studied in 122 adult asthmatics with a mean FEV₁ of 63% predicted and using an average of 5.8 puffs/day of short-acting β_2 -agonist at baseline. (29) The FEV₁ increased after the first doses of zileuton and remained improved over the 6-month study period (Table 1). Subjects receiving zileuton had fewer asthma symptoms, lower requirements for short-acting β_2 -agonist or corticosteroids rescue, and fewer asthma exacerbations.

Overall, LT modifiers have been demonstrated to improve asthma control with improved pulmonary function tests and reduction of symptoms in patients with mild-to-moderate disease who are receiving short-acting β_2 -agonist only. However, the clinical benefits of LT modifiers achieved in placebo-controlled trials are generally modest and monotherapy with these agents is most likely insufficient to achieve the goals of asthma care in patients with moderate or severe asthma.

Comparative Clinical Trials.

The effects of montelukast 10 mg once daily, placebo, and beclomethasone 200 mcg twice daily were evaluated over 12 weeks in 895 patients with moderate asthma (FEV₁ 50-85%, mean 66%, mean short-acting β_2 -agonist use 5.5 puffs/day). (34) Patient response to montelukast or beclomethasone was superior to placebo and the effect of beclomethasone was superior to montelukast. Mean response differences between beclomethasone and montelukast were 5.8% for FEV₁, -0.67 puffs/day for β_2 -agonist use, and -0.7 nights/week for nocturnal awakenings favoring beclomethasone. Montelukast had a faster onset of action (within one day); however, the effects of beclomethasone surpassed that of montelukast after 7 to 10 days of therapy. The incidence of adverse effects was reported to be similar in the three treatment groups. In a 3-week washout period at the end of the

study, there was no apparent rebound worsening of asthma symptoms and FEV₁ values returned to baseline in patients receiving montelukast or beclomethasone who were switched to placebo.

Using an intention-to-treat study design, the steroid-sparing effect of montelukast 10 mg once daily was evaluated in 226 asthmatics aged 17-70 years with an FEV₁ >70% (mean 84%) requiring moderate to high doses of inhaled corticosteroids (300-3000 mcg daily) (35). Dosages of inhaled corticosteroids were tapered over 6 weeks before entering a 12-week period of double-blind treatment. Inhaled corticosteroid dose was adjusted every two weeks according to a composite clinical score. Twenty-one percent of patients (48/226 patients enrolled) did not complete the 12-week period. Montelukast therapy was associated with a reduction in the mean inhaled corticosteroid dose from 976 mcg/day to 526 mcg/day (47% absolute reduction) compared with placebo (from 1079 mcg/day to 727 mcg/day; 30% absolute reduction), without significant changes in FEV₁, asthma symptoms, and β_2 -agonist use. Those patients receiving montelukast had fewer failed rescue episodes (16% vs. 30% with placebo; $p=0.01$). Failed rescue episodes were defined as the number of patients who failed to regain clinical stability after an increase in dose of corticosteroids. This study suggests that montelukast may have a steroid-sparing effect, although the absolute difference in the reduction of corticosteroid dose at the end of 12 weeks appeared to be small (absolute difference of 98 mcg/day or 17.6%; 95% CI: 0.3 to 34.8%; $p=0.046$). Considering the wide 95% CI and the proximity of the lower limit to zero, it is difficult to establish a clinically relevant difference compared to placebo. Differences in potencies between various inhaled corticosteroids were not taken into account when comparing the percentage change in the corticosteroid dose. Finally, the number of patients on different types of inhaled corticosteroids was not reported and equivalent doses were not calculated when comparing groups.

A clinical trial examined the use of montelukast 10 mg once daily in combination with beclomethasone 200 mcg twice daily to determine whether concomitant therapy would yield additional clinical benefits in

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patients with incompletely controlled asthma (36). Overall, 193 patients were randomly allocated to the montelukast plus beclomethasone group and 200 patients were assigned to the beclomethasone group (placebo tablets once daily and inhaled beclomethasone 200 mcg twice daily). At baseline, patients in both groups had a mean FEV₁ of 71.5% and reported to use about 3.5 puffs/day of short-acting β_2 -agonist. Primary endpoints that were measured in the study were FEV₁ and patient-reported daytime asthma symptoms. The addition of montelukast resulted in improvements in FEV₁ (5.08% vs. 0.72% in the montelukast plus beclomethasone and beclomethasone only groups, respectively, $p < 0.001$), daytime asthma symptom scores (-0.13 vs. -0.02, respectively, $p = 0.041$) and nocturnal awakenings (-1.04 vs. -0.45, respectively, $p = 0.010$); however, total β_2 -agonist use was similar in both groups (-5.51% change from baseline vs. 6.04; $p = 0.08$). Montelukast provided additional clinical benefits; however, inclusion of a group on a higher dose of inhaled corticosteroids would have been of interest to determine whether the addition of montelukast is comparable in efficacy to increased doses of corticosteroids.

The efficacy of zileuton was compared with theophylline (target trough serum concentration between 8-15 mcg/ml) in 377 adult asthmatics (mean FEV₁ about 60% predicted) using approximately 6.5 doses of β_2 -agonist daily (37). After 13 weeks of treatment, FEV₁ measurements were similar in patients receiving zileuton and theophylline (increase from baseline of 30.2% vs. 33.7% with zileuton 2.4 g/day and theophylline, respectively). Improvement in morning and evening peak flow measurements, β_2 -agonist requirements (decrease of 1.5 puffs/day vs. 2 puffs/day with zileuton 2.4 g/day and theophylline, respectively), use of rescue corticosteroids, symptom and quality of life scores were not different in subjects on theophylline and zileuton. Overall, the efficacy of zileuton and theophylline was similar in patients with mild-to-moderate asthma.

The efficacy of salmeterol 42 mcg twice daily and zafirlukast 20 mg twice daily was compared over a 4-week period, in a 189 adults with persistent asthma (FEV₁ 50-80%, mean 68%) (38). Approximately 80% of

patients in each treatment group were receiving a stable regimen of inhaled corticosteroid at the time of study enrolment. Overall, salmeterol provided greater improvements in pulmonary function and symptom control. Salmeterol increased morning peak flow (primary endpoint) by 29.6 L/min while zafirlukast improved this value by 13.0 L/min. Zafirlukast and salmeterol provided similar improvements in FEV₁, nocturnal awakenings, β_2 -agonist use and asthma exacerbations. The incidence of adverse events was similar in each treatment group. This study was the first published report in which the efficacy of salmeterol and zafirlukast were compared directly. Even though most patients were receiving inhaled corticosteroids, the use of salmeterol is not recommended without concomitant inhaled corticosteroids. Both treatment groups were comparable at baseline, but the dose of inhaled corticosteroid received during the study was not specified. Finally, this short-term trial is not sufficient to draw conclusions about the efficacy of one agent over the other as an add-on therapy with inhaled corticosteroids. Long-term trials are required to characterize the efficacy of long-acting β_2 -agonist over LT modifiers in chronic asthma management.

Aspirin-Intolerant Asthmatics

The efficacy of zileuton was evaluated in a cross-over study of 40 aspirin-intolerant asthmatics (AIA). (39) Most patients were receiving corticosteroids at baseline. Zileuton improved FEV₁ (difference with placebo after 6 weeks of treatment: 0.19 L; $p < 0.01$), reduced daily β_2 -agonist use (difference with placebo of 0.64 puffs/day; $p < 0.05$), and lowered the scores for loss of smell and rhinorrhea. However, asthma symptoms, peak nasal inspiratory flow rates and nasal congestion scores were similar with zileuton and placebo.

Safety

The incidence of adverse effects is mostly similar in patients receiving LT modifiers and placebo in the clinical trials reviewed. An exception to this is the reversible elevations in liver function tests seen in 2-

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9% of patients in studies of zileuton (28,29). One patient experienced jaundice, hives, and increased liver function tests, which resolved after discontinuation of zileuton (28). Patients on zileuton should have liver function tests performed before starting therapy, every month in the first three months, every 2-3 months for the rest of the first year of treatment, and periodically thereafter (10). Infrequent asymptomatic elevations in serum liver enzymes has been reported with higher than recommended doses of zafirlukast (7).

Concern about the association between Churg-Strauss syndrome and the use of LT modifiers has been raised. Churg-Strauss syndrome is an eosinophilic vasculitis that has been reported in patients with moderate or severe asthma receiving zafirlukast and montelukast. Most patients were undergoing corticosteroid withdrawal after the addition of a LT modifier. It has been postulated that this reaction is not directly related to LT modifiers, but may be an unmasking of the syndrome following corticosteroid withdrawal. A causal relationship between this syndrome and LT modifiers remains unproven and the occurrence of this event is rare (40). Patients with moderate to severe asthma should be monitored for signs and symptoms of the Churg-Strauss syndrome when corticosteroids are tapered or discontinued following the addition of a LT modifier. Leukotriene modifiers are generally well tolerated, but there is limited experience with long-term use of these agents

Discussion

The role of LT modifiers in asthma management is currently being defined. The Expert Panel of the National Asthma Education and Prevention Program states that zafirlukast and zileuton (montelukast was not available at the time of writing of the Expert Panel Report) should be considered as alternative long-term therapies to low-dose inhaled corticosteroids, sodium cromoglycate or nedocromil for patients with mild persistent asthma, but the place of LT modifiers in asthma therapy has not been entirely established (41). The 1999 Canadian Asthma Consensus Report describe the role of LT modifiers as an alternative

to low-dose inhaled beclomethasone in patients with mild asthma who cannot tolerate or choose not to use inhaled corticosteroids, although no studies in this population have been published; as an alternative to increased doses of inhaled corticosteroids or as an alternative add-on therapy in place of long-acting β_2 -agonist (1). Unfortunately, few comparative trials are available. To further define their place in therapy, trials comparing LT modifiers with standard therapy, such as inhaled corticosteroids in mild chronic asthma; long-acting bronchodilators in moderate-to-severe asthma; and comparisons to higher doses of inhaled corticosteroids in moderate-to-severe asthma are required. Relevant studies should evaluate primary clinical endpoints that include oral steroid rescue, unscheduled medical visits, hospitalizations, and asthma exacerbations. These trials are underway and their results may enable clinicians to rank LT modifiers within the armamentarium of asthma therapies.

Leukotriene modifiers differ in terms of frequency of administration, whether they can be taken with food or not, in their safety profile and in their potential for drug interactions. Zileuton is given four times daily, whereas zafirlukast is administered twice daily and montelukast once daily. Zileuton and montelukast may be administered without regards to meals, whereas zafirlukast must be taken on an empty stomach. Zileuton may cause hepatic toxicity and unlike other agents, periodic monitoring of liver function tests is necessary. Zileuton and zafirlukast may influence the elimination and clinical effects of other medications (e.g. warfarin) whereas no drug interactions have been identified with montelukast to date. Finally, whether one agent is superior to another is unknown since no clinical trials have directly compared the efficacy of leukotriene modifiers. Overall, montelukast has many advantages over other agents of this class and may be the LT modifier of choice.

Leukotriene modifiers provide additive benefits to inhaled corticosteroids. In clinical practice, these agents are used in combination with other therapies (i.e. medium or higher doses of inhaled corticosteroids) as an alternative to increasing the corticosteroid dose, or to reduce the corticosteroid dose required to

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maintain asthma control. Leukotriene modifiers are usually considered as second-line adjunctive therapies to moderate or higher doses of inhaled corticosteroids since more data and clinical experience are available with using long-acting β_2 -agonist. Because they reduce LT-induced airway inflammation, LT modifiers should be the treatment of choice in patients with mild persistent asthma who choose not to use inhaled corticosteroids. Inhaled corticosteroids may prevent the decline in lung function that occurs in patients with asthma, whereas the effect on airway remodeling has not been confirmed with LT modifiers (1). Monotherapy with LT modifiers is insufficient to achieve the goals of asthma therapy in patients with moderate or severe disease.

Clinical trials evaluating montelukast in exercise-induced asthma have demonstrated that it is useful for this indication when used on a regular basis (24,42-45). Leukotriene modifiers are of particular interest in patients with aspirin-induced asthma, which involves a LT-mediated process, but comparative trials remain to be completed. These agents currently have no role for the acute management of asthma exacerbations. Finally, the use of LT modifiers is pregnancy and lactation is not recommended at this time since human data is not available and clinical experience is limited (45).

Leukotriene modifiers have the advantages of being administered orally, of having few side effects and, in the case of montelukast, having no drug or food interactions. Unfortunately, asthma control is not improved in all patients receiving LT modifiers. It appears that only 30-50% of patients will respond to therapy, and characteristics that predict response are unknown. Since LT modifiers have a rapid onset of action, a 2-week trial is generally sufficient to determine if patients will benefit from therapy. An exception is when LT modifiers are used in an attempt to reduce the corticosteroid dose, where the trial period is usually longer.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2000;1:400.

A Retrospective Evaluation of the Management of Skin and Soft Tissue Infections in the Emergency Department

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University of British Columbia Pharmacy 405 (Directed Studies) Research Presentation Seminar (Podium presentation). Vancouver, British Columbia, Canada. April 7, 2000. (Unfunded study).

Context

Skin and soft tissue infections (SSTI) are commonly managed in an Emergency Department (ED) setting. Prior to the study, the outpatient intravenous (IV) antibiotic program at this major teaching hospital operated without any set protocol with respect to inclusion/exclusion criteria, treatment guidelines, and clinical pathways. The objective of this study was to evaluate the management of SSTI in the ED, in order to determine the therapeutic implications of implementing a new treatment program.

Design

Retrospective health record assessment for selected patients evaluating two 6-month treatment periods pre- and post-implementation of the new program.

Setting

Emergency Department of a major Canadian tertiary care teaching hospital.

Subjects

Adult patients with SSTI (as diagnosed by emergency physicians and entered into the outpatient IV antibiotic program)

Intervention

The pre-protocol management of SSTI was left at the discretion of the attending emergency physician.

The outpatient IV antibiotic program for SSTI utilized standardized protocols for both intravenous and oral therapy. Cefazolin 2 g IV every 24 hours with probenecid 1 g PO daily is the mainstay of therapy for simple cellulitis. Ceftriaxone 2 g IV every 24 hours was the therapy of choice for those with SSTI resulting from a cat, dog or human bite wound. Oral (PO) regimens for step-down therapy were also included in the new program protocol for all SSTI. The optimal treatment duration in the outpatient program was defined as less than or equal to 5 days.

Main Outcome Measures

The primary outcome was clinical treatment success defined as successful treatment in the outpatient program utilizing either (i) PO therapy alone; (ii) IV therapy alone; or (iii) IV to PO stepdown following resolution of infection. Secondary outcomes included compliance with the new protocol, overall treatment duration as well as appropriate use of recommended IV to PO step-down therapy.

Results

428 patients (211 pre and 217 post) met our pre-defined inclusion criteria for the 12-month study period. Simple cellulitis was the most common diagnosis between phases at 91% and 89%, respectively; and IV cefazolin and PO probenecid combination was the primary treatment regimen in both phases at 86% and 83%, respectively. Overall treatment success was similar in both periods at 86% and 81% respectively. Overall, compliance with the new outpatient program protocol was 96% with a significant improvement in the use of appropriate IV to PO therapy from 21% pre-protocol to 60% post-protocol. Overall, 89% of patients were successfully treated in the ideal program duration of less than or equal to 5 days in following implementation of the new program.

Conclusions

The use of a standardized protocol for the outpatient management of SSTI from the ED has proven effective resulting in the prevention of many hospitalizations.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2000;1:401.

Prevention and Conversion of Post Cardiac Surgery Atrial Fibrillation: A Systematic Review of Antiarrhythmic Interventions

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Context

Atrial fibrillation (AF) is a common complication following cardiac surgery and has a significant impact on symptoms, hemodynamics, morbidity, and health-care costs. There is no consensus on the optimal use of antiarrhythmic interventions for the prevention and treatment of post-cardiac surgery AF (PCSAF).

Objectives

A qualitative systematic review was conducted to determine the most effective currently available antiarrhythmic agents for the prevention and pharmacological conversion of PCSAF.

Search Strategy

Articles indexed in MEDLINE (1966 to present), EMBASE (1988 to present) and CURRENT CONTENTS and reference lists of identified articles and review articles were searched.

Selection Criteria

English language trials describing the use of antiarrhythmic drugs for the prevention or treatment of PCSAF were identified and reviewed. Exclusion criteria included previously published data, data published only in abstract form, unpublished data, and studies including only agents not available in Canada.

Data Collection and Analysis

Three reviewers independently extracted data and assessed the quality of the trials based on an arbitrary levels of evidence scheme.

Main Results

Fifteen published prevention trials were identified and 10 involved a prospective (P), randomized (R), placebo-controlled (PC) design. Sotalol (NNT=3), and oral amiodarone (NNT=8) were more effective than placebo as pre-op/post-op prophylaxis. Sotalol (NNT=8-9) and IV amiodarone (NNT=8) were more effective than placebo as post-op prophylaxis. Nine published treatment trials were identified and 3 were based on P, R, PC trials. Ibutilide was the only agent significantly more effective than placebo at converting AF to normal sinus rhythm.

Conclusions

There is a lack of well-designed clinical trials examining the use of antiarrhythmic therapy for the prevention and treatment of post-cardiac surgery AF. Both sotalol and amiodarone initiated pre- or post-operatively reduce the incidence of PCSAF. Only ibutilide effectively converts PCSAF to NSR. Prophylaxis studies comparing antiarrhythmics to beta blockers or evaluating antiarrhythmics plus beta blockers, and adequately powered treatment studies evaluating IV procainamide, IV amiodarone, and oral propafenone are needed.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2000;1:402.

Outpatient Treatment of Deep Vein Thrombosis from the Emergency Department: Clinical Outcomes, Patient Satisfaction and Economic Analysis

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Context

Low-molecular-weight heparins (LMWH) have been shown to be safe, effective and economically attractive for the outpatient treatment of deep vein thrombosis (DVT). The Vancouver Hospital and Health Sciences Centre (VHHSC) outpatient DVT program was implemented in June, 1999 to take advantage of this safe, effective and economically attractive therapy. The objective of this study was to: (i) determine if the VHHSC outpatient DVT program is safe and effective; (ii) to assess the economic impact compared to inpatient management and; (iii) to evaluate patient satisfaction with the outpatient program.

Design

Prospective non-comparative clinical trial combined with a pre/post economic assessment and post-intervention patient satisfaction survey.

Setting

Emergency Department of a major Canadian tertiary care teaching hospital.

Subjects

Patients were enrolled in the outpatient program if they had a radiographically-diagnosed DVT by an

emergency physician.

Intervention

Eligible patients returned daily to hospital to receive tinzaparin 175 u/kg sc for a minimum of 5 days and warfarin until INR >2 on two consecutive days at which time they were discharged to the care of their family physician.

Main Outcome Measures

Clinical evaluation of efficacy was prospectively evaluated by the incidence of recurrent venous thromboembolic events (RVTE) at 3 and 6 months while safety was determined evaluating bleeding complications and thrombocytopenia. Economic assessment was determined by comparing total costs of therapy for each outpatient determined prospectively, to data collected retrospectively from inpatients treated with unfractionated heparin and warfarin. Patient satisfaction in the outpatient DVT program was established by a 19-question mail-out patient satisfaction survey.

Results

Twenty-five patients were treated in the program for a mean length of treatment of 6 days. No RVTE were identified in patients who had reached 3 and 6 months evaluation post discharge. No patient experienced a major bleeding complication or developed thrombocytopenia while 2 patients experienced a minor bleed (epistaxis & hematuria). Average cost/treatment/inpatient was \$2214.99 (CAN) compared to \$573.00 (CAN) for outpatient therapy, representing a cost savings of \$1641.99 (CAN) for every DVT treated using the outpatient DVT program. Overall, 76% of patient satisfaction surveys were returned and indicated that 90% of patients were very satisfied or satisfied with the outpatient program.

Conclusions

This outpatient DVT program is safe, effective, economically attractive and is well-received by the patients enrolled.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2000;1:403.

Patient Preferences & Quality of Life Assessment for Outpatient Parenteral Antibiotic Therapy (OPAT) in the Home Setting: A Preliminary Analysis

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night (Podium and Poster presentation). Vancouver, British Columbia, Canada. May 10, 2000. (Unfunded study).

Context

Select inpatients are candidates for parenteral antimicrobial therapy in the home setting. To facilitate this type of treatment delivery, we introduced an Outpatient Antimicrobial Treatment (OPAT) Program at Vancouver Hospital and Health Sciences Centre in 1995. Satisfaction surveys collected over the ensuing years have shown favourable patient response; however no in depth evaluation has been accomplished. To our knowledge, there are no published formal assessments of patient preferences and quality of life of patients enrolled in an OPAT Program. The objectives of this study were to measure patient preference and willingness to pay for treatment setting and to measure change in quality of life for patients enrolled in this OPAT Program.

Design

A prospective single centre survey-based study involving contingent valuation (willingness to pay) and quality of life questionnaires.

Setting

A major Canadian tertiary care teaching hospital.

Subjects

Adult inpatients who were candidates for the OPAT program were considered eligible to complete the willingness to pay (WTP) questionnaire. Patients enrolled in the OPAT program were considered eligible to complete the quality of life assessment. All participants provided informed consent.

Intervention

During the initial 7-month study period, consenting OPAT Program candidates completed the WTP questionnaire. Marginal willingness to pay for preferred treatment location (hospital versus home settings) was assessed using hypothetical scenarios outlining the probabilities of various outcomes for each location. Those consenting patients who were subsequently enrolled in the OPAT program also completed a Short Form-36 (SF-36) questionnaire for the quality of life assessment component of the study. This latter instrument was administered prior to discharge and repeated 4 weeks later.

Main Outcome Measures

Patient preference for treatment setting, willingness to pay for this preferred treatment setting, and changes in the patient's reported quality of life.

Results

Of the initial 67 patients surveyed, 83% reported a preference to be treated in the home setting while 13% preferred to remain in hospital. The balance had no preference. Fifty-two patients provided an interpretable response to the WTP scenarios with a mean of \$1,076 and median of \$470 (range \$10-\$6,250). While role-physical and general health domain scores tended to decline; bodily pain, social functioning and role-emotional scores improved subsequent to discharge. Most domain scores were below the published U.S. population averages with the exception of mental status.

Conclusions

Preliminary data suggests that most adult inpatients in our hospital with infections prefer to be treated in the home setting and are willing to pay for this preference. Quality of life appears to improve for patients who are enrolled in the program and discharged home, but this seems to be domain-dependent.

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Updated
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Editorial

Medical Informatics: Meeting the Information Challenges of a Changing Health Care System

The major dilemma facing medical science at the beginning of the 20th Century was the lack of biomedical knowledge. The major dilemma facing us at the dawn of the 21st Century is the application of biomedical knowledge. Health care is a prototypical knowledge business, but it is also perhaps the most complex of all knowledge industries. The growing complexity of the information base and the explosion of biomedical information contribute to the decay rate of scientific knowledge acquired during a typical health sciences education. The National Library of Medicine's *Medline* archives 31,000 new citations per month and it is now estimated that a clinician needs to read 17 articles a day every day of the year simply to remain current in their field of practice. (1,2) Whether it is practiced at the bedside or managed in the boardroom, health care is an information intensive industry.

Clinicians create, use and promulgate information. To be effective caregivers, researchers, and health educators therefore depends increasingly on our abilities to manage information. However, simply adopting information technologies (IT) is not enough. Just as the ability to use a stethoscope does not make one a physician, the ability to use IT or "surf" the Internet does not imply that one understands the principles and nuances of information or information management.

Information and technology are quintessential human creations and thus require humans as managers. Because of this, information can be analyzed from ecological perspectives. (3) Approaching information and information management in this fashion emphasizes an organization's entire information environment. This approach avoids the pitfalls of over-focusing on technology. The ecological perspective of information allows an organization to think holistically about information management and to focus on the four key attributes of the ecology: 1) information is diverse; deriving from disparate sources and thus must be integrated; 2) information evolves with each new discovery or inquiry; information management must evolve with the information itself; 3) information and the use of information can be observed and described; 4) there are behavioral aspects attributed to information. Simply put, this refers to how individuals or organizations approach and handle information. Effective clinical information management requires every clinician to understand these principles. It also requires an understanding of data interpretation, the logical foundations of clinical reasoning, the recognition of uncertainty in clinical knowledge, and the local politics and strategic vision or lack of surrounding information.

The task for informaticists is to design the information resources and systems that enable health care providers and organizations to recognize and create information ecologies in

their practice settings. Broadly defined, informatics is concerned with the incorporation of IT into the day-to-day workflow and delivery of health care. To accomplish this, informaticists must deal with the uncertainty of the clinical encounter, the expansion of clinical information, the complexity of the health care delivery setting (clinical and financial), the limited ability of the human mind to simultaneously utilize four to seven data constructs, and the explosion of technology itself. (4) In effect, medical informaticists spend their careers studying the mechanics of medical information and medical reasoning, the abstraction and elaboration of knowledge, and the processes of memorization and learning. To that end, medical informatics is a scientific discipline with its roots in information theory. Medical information is characterized by its subject matter (i.e. medicine) and its methodology (i.e. information management). The discipline draws on other sciences such as mathematics, cognitive psychology, statistics, linguistics, philosophy, and computer science. Applications derived from medical informatics research allow us to provide knowledge about knowledge and therefore, it embodies all areas of the health sciences, from the microscopic to the macroscopic, and from the individual patient to society. Clinical informatics is a subset of medical informatics and is mainly concerned with clinical practice and the information management issues contained therein. (5) Clinical informatics is to medical informatics as clinical epidemiology is to epidemiology in general.

Social, financial, and technical forces originating within and outside the health care field are exerting tectonic changes. Medical informatics is a field of growing importance as the health care industry struggles to adapt to these changes. Informaticists are best suited to understand the nature of biomedical information, the working conditions of health care providers, and the information systems themselves. Medical informatics is being recognized as central to the mission of surviving in these turbulent times and will be the springboard from which practitioners of medicine, pharmacy, nursing, and dentistry will derive clinical applications to better serve their patients and society.

Given these realizations, should pharmacists be retrained as medical informaticists? Certainly, the technologies that medical informaticists develop such as clinical decision support systems will change the way the profession delivers care and the role of the pharmacist in that delivery. Pharmacists are particularly vulnerable to the impacts of clinical decision support systems. These tools will replace many of the current cognitive contributions of pharmacist clinicians, however they will also spurn unimaginable opportunity. Domain specialists are key to the content development required for clinical decision support systems. Pharmacists are natural domain specialists given their fundamental body of pharmacotherapeutic knowledge and are well positioned to play key roles in the development of clinical decision support systems. It would be wise for pharmacists to become familiar with techniques, such as knowledge engineering and to develop relationships with medical informaticists. These relationships will establish a vital role for pharmacists in the design and implementation of clinical decision support systems. A proactive role of pharmacists in these developments will allow the profession to define its roles and direct its destiny.

In this issue of the Journal, Balen et al. provide us with an interesting Canadian perspective on the issue of pharmacists' clinical informatics needs and their applications

in practice. (6) These practitioners review essential clinical informatics skills, provide some good examples of effective informatics use in everyday practice and describe their recent efforts towards enhancing pharmacy student knowledge on this topic. I'm sure the authors would agree with me that we live in marvelous times; we just need to be organized to take full advantage of what is now available to us.

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J Inform Pharmacother 2000;2:1.

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Issues in Pharmacotherapy Practice

Medical Informatics: Pharmacists' Needs and Applications in Clinical Practice

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Abstract

Pharmacy is an information intensive profession. The information explosion and the emphasis on evidence-based medicine are forcing changes in pharmacists' roles. Affordable computers combined with the advancement of information technology can now provide extremely useful clinical applications for pharmacists in their own working conditions. Computers can enhance practice by providing a rapid and effective means of accessing, retrieving, analyzing, sharing and storing large volumes of information pertinent to patient care. Several examples of the effective use of informatics tools in a hospital intensive care unit are presented such as: rapidly retrieving information to solve an urgent case; creating a personal Internet library, efficiently browsing the Internet, using computerized patient care worksheets and integrating hand-held portable computing tools into the pharmaceutical care process. These examples can be applied to any practice setting. Informatics is an emerging academic discipline in the health sciences. Essential informatics skills for pharmacists are reviewed. We describe a proposed medical informatics syllabus for the clinical pharmacist to provide the knowledge and skills in informatics essential for today's practice.

J Inform Pharmacother 2000;2:306-318.

Introduction

Pharmacy is an information intensive profession that demands effective use of technology to manage an ever-expanding body of knowledge. "Information anxiety" is described as the frustration of being inundated by an overabundance of information sources while being unable to navigate them to find specific needed information. (1) In order to minimize information anxiety, pharmacists must be competent in the use of computers to collect; store, retrieve and send drug and patient related data for both administrative and clinical purposes. The importance of information technology to the future of pharmacy practice has been well described in the literature. (2-5) Information technology has always influenced pharmacy practice, but now with the availability of inexpensive yet powerful computers

and rapid communication via the Internet and other networks, this technology will exert an increasing force in changing roles for pharmacists. An understanding of some information technology principles may help practitioners avoid being "buried alive" in the streams of data that now permeate the health care setting. (6)

The term *medical informatics* has been defined as "the field concerned with the cognitive, information processing, and communication tasks of medical practice, education, and research, including the information science and technology to support these tasks." (1) The informatics field also includes advanced research initiatives that can be used in clinical practice including: i) expert clinical decision analysis and decision support initiatives (7-11); ii) electronic medical records (12); iii) data warehousing and analysis of collaborative data sets (13,14); iv) computer automated drug interaction, adverse drug reaction and drug usage monitoring systems (15-17) and; v) telecommunication advances such as video conferencing via Internet and intranet connected systems. (2) Advancements in hospital decision support systems and electronic medical records have been slow and are not as yet widely used as these systems have been more difficult to implement than previously anticipated. (2,18) There are; however, currently available off-the-shelf technologies that can be utilized by individual clinical practitioners. It would be prudent for all clinicians to familiarize themselves with these resources and learn how to apply them to their practice in a practical fashion. Primers on Internet use and online clinical resource utilization regularly appear in the medical literature. (19,20)

Pharmacists need to develop a set of practical informatics skills to manage the data and information challenges in their practice. This article focuses on some available computer resources that can augment clinical practice. Informatics skills considered essential for pharmacists to learn and examples of how these skills apply to clinical practice are provided.

Essential Informatics Skills for Pharmacists

The evidence-based practice paradigm increases clinician information needs and to meet these needs, clinicians require rapid access to resources that provide content that is relevant, valid, and can be obtained with minimal effort. (21) Ideal information resources are electronic, portable, connected to valid databases and servant to the user. (21-23) While pharmacists may not need to be experts in information systems, they do need sophisticated end-user knowledge of technologies that are available and applicable to research and clinical practice. These technologies include personal and network computing; hospital information systems; personal digital assistants; the Internet; word processing; and presentation, statistical analysis and database management software. Those practitioners who do not incorporate some of these tools into their practice will undoubtedly have difficulty keeping up with the clinical information necessary for evidence-based practice. As other health care professionals continue to incorporate available technology into their practices, pharmacists need to advance at least as quickly to ensure that they are at the forefront of this movement. Only by doing so will they be able to ensure that they continue to be the drug expert in the health care team. The development of automated drug dispensing, clinical monitoring and clinical decision support systems is evolving rapidly and these developments challenge the pharmacist to maintain an evidence-based and patient-centered role in the healthcare system.

Essential clinical informatics skills have previously been identified from a medical perspective. (24) Coiera proposes that, in addition to having basic computer skills, ten essential clinical informatics skills are needed in order for clinicians to properly manage information (Table 1).

Upon reviewing the American College of Clinical Pharmacy position statement describing the practice guidelines for a pharmacotherapeutic specialist, one could infer that many of these same skills are integral to pharmacy practice. (25) It is clear that effective information management requires more than basic computer literacy. Computer skills are fundamental to integrating technology and clinical practice and to facilitating the effective transformation of data to useable clinical information.

Table 1: Ten Essential Clinical Informatics Skills (24)

-
1. Understand the dynamic and uncertain nature of medical knowledge and know how to keep personal knowledge and skills up-to-date.
 2. Search for and assess knowledge according to the statistical basis of scientific evidence.
 3. Understand some of the logical and statistical models of the diagnostic process.
 4. Interpret uncertain clinical data and deal with artifact and error.
 5. Analyze and structure clinical decisions in terms of risks and benefits.
 6. Adapt and apply clinical knowledge to the individual circumstances of patients.
 7. Access, assess, select and apply a treatment guideline; adapt it to local circumstances; and communicate and record variations in treatment plan and outcome.
 8. Structure and record clinical data in a form appropriate for the immediate clinical task, for communication with colleagues, or for epidemiological purposes.
 9. Select and utilize the most appropriate communication method for a given task (e.g. face-to-face conversation, telephone, e-mail, video, voice-mail, letter).
 10. Structure and communicate messages in a manner most suited to the recipient, task and chosen communication medium.
-

Student and Clinicians Needs for Informatics Training

Medical Informatics is fervently being addressed as an emerging academic discipline in medicine, nursing and dentistry. (1,26,27) Many medical schools and residency programs are including informatics training in their programs.(28-33) Dentistry schools likewise consider informatics essential in their training.(34,35) Nursing has developed informatics to the point of debating "nursing informatics" as a distinct discipline. (36-40) Pharmacy is certainly one of the most information-intensive professions and yet we have not taken the lead in developing informatics specific for our needs and where medicine and nursing needs overlap ours. Currently there is a lack of research addressing informatics needs in any area of pharmacy practice and pharmacy education.

Certainly anxiety is produced by the continuous statements that health care technology will change the role of pharmacists and create expanded opportunities for pharmacists in the future. Unfortunately such statements about future capabilities of technological advances do nothing to aid in defining what the roles will be or how to get there from our present state. Now that computer equipment has finally reached a stage of being affordable, user friendly, and that evidenced-based information is readily available and easily accessed via the world wide web, we felt it was urgent to develop an informatics course for undergraduate pharmacy students. While a number of organizations have developed recommendations for medical informatics education, none are directed specifically for pharmacists needs. (41-44) Upon accepting the reality that health care technology is in a state of rapid transition, we attempted to design an essential informatics knowledge and skills course for a clinical pharmacy practitioner today. The central guiding question was how could computers be used to make the clinical pharmacists' role easier yet more effective in improving patient care? The overall goals of the course that we propose are: 1) to develop an awareness of the usefulness and limitations of computers and informatics tools in pharmacy practice; 2) to demonstrate and facilitate the development of essential skills for the use of technology to meet the increasing and evolving demands of pharmacy practice today; 3) to provide a framework for life-long technology-assisted continuing education and clinical practice; and 4) to develop an appreciation of the impact of automation on pharmacy practice. Our proposed syllabus includes computer literacy, and software applications; communication via the Internet; pharmacy automation; and information management. Throughout the development of this syllabus we attempted to prioritize topics that are applicable in practice today and yet remain comprehensive in the variety of informatics topics addressed.

Currently there exists great interest in learning about informatics. This was revealed in a recent continuing educational needs survey of 2,500 Canadian physicians in general or family practice. (45) This survey revealed that almost 55% of respondents selected informatics and computers over other professional or clinical options as the highest priority topic for improvement in knowledge and skills. Interestingly, 63% of respondents indicated that they had no access to computer support for practice. This confirms our experience that there is a recognized interest in informatics training. Over the past year, we have had many requests from pharmacy students, faculty, pharmacists and family physicians to be taught informatics skills. Consequently we have given separate presentations encompassing introductory applied informatics material for both pharmacy students and family physicians in both university-based and hospital-based computer labs. These sessions have resulted in numerous requests for additional training topics. Based upon our personal experience, the perception that the majority of health professionals has access to and use information readily available through computers is not a reality. The challenge of educating future and current health professionals in informatics must be addressed now.

Examples of the Effective Use of Informatics Tools in Everyday Practice

Here are some practical examples how readily available computer hardware and software can be integrated into every day clinical practice.

Rapid Retrieval of Drug Information

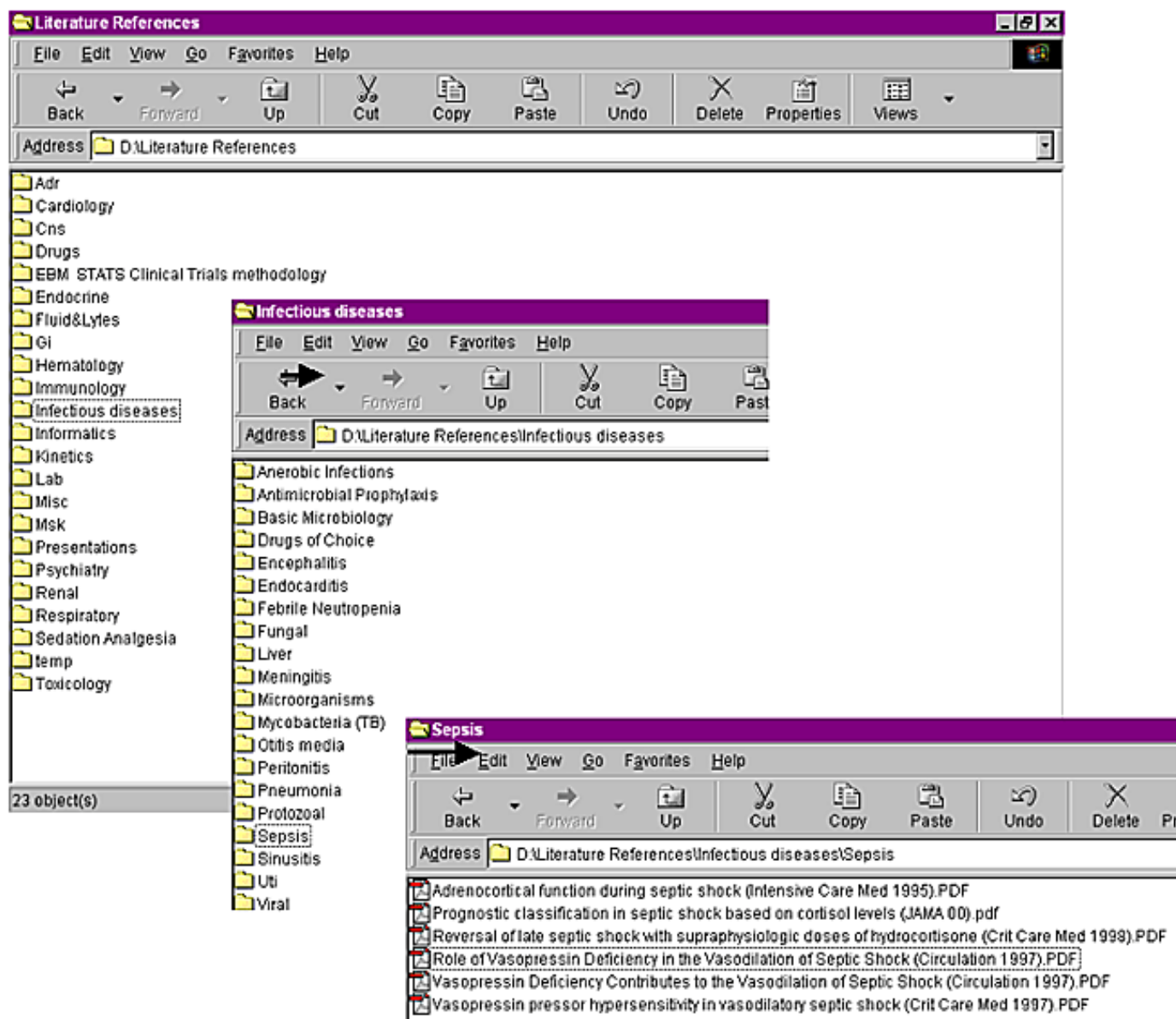
You are in the Intensive Care Unit preparing for morning interdisciplinary rounds. The patient just admitted to Bed-1 is a 38-year-old female with septic shock secondary to bacteremia. The patient has multiple loculated hepatic abscesses and is receiving high doses of inotropic drugs. Fluid balance has been optimized and she is maintaining a mean arterial pressure of 55 mmHg with a regimen of dopamine 20 mcg/kg/min and norepinephrine 20 mcg/min. You have been keeping up with the critical care literature and realize that a viable therapeutic alternative for pressor support in this patient may be a vasopressin infusion. Rounds start in 5 minutes and you can't remember the dosing protocol nor the specific inclusion criteria reported for the studied patient population. You know that you have the relevant papers in your "files" somewhere but locating them will likely take some time.

This is a common scenario for all practicing clinicians who need to have rapid access to previously retrieved reference material that is now located in personal library files. One potential solution to this problem is to create your own digital library that is portable and readily accessible. Resources are available to electronically file publications. Many journals are now available on-line with full text access to personal and institutional subscribers. Journal articles that are not available online can be converted to electronic format with a scanning device and the appropriate file storage software. Key articles can be made readily retrievable by electronically filing the digital version on your computer or a network hard drive. A common format for digital document distribution is the portable document format ("PDF") that has been created by Adobe Systems Inc. (<http://www.adobe.com>). Portable document format files can be read by anyone who has installed the free reader software. These files can be stored locally and organized in a directory structure that is logical to the user such as a head-to-toe systems approach. Adding relevant PDF format journal articles takes seconds with basic file management techniques. The advantage of having your personal reference files stored digitally is that you can quickly access the files from your PC or any networked PC in your hospital.

Revisiting the above case scenario, 5 minutes is ample time to log on to a networked PC, locate and retrieve your relevant files pertaining to the use of vasopressin for septic shock and be prepared for a bedside discussion about the possibility of instituting this mode of therapy. Occasionally it may be difficult to recall the folder in which the file is located. In such cases, the "find file or folder" function of your computer operating system can be used to

search your references by file name. This will provide you with a list of the relevant files on your computer. Some third party file indexing software can be used to search your files by key words throughout the text of the document. An example of the authors (RMB) networked electronic library pertaining to the above case scenario is outlined in Figure 1. Once located, the relevant paper can be printed or viewed on screen.

Figure 1. Directory structure of a digital reference library on a personal computer



Integrating on-Line Resources into your Daily Practice

A family physician calls you asking about pharmacotherapeutic options to assist in removing a Bot Fly that is embedded in a patient's scalp. The patient is a 40-year-old botanist who was contracted to do some work on a farm in Central America. Upon returning home she was noted to have a swollen 2 cm diameter itchy boil-like erythematous area on top of her head. Being familiar with the parasite hazards in Central America and having experienced Bot Fly problems in the past, the patient was suspicious about this itchy area on her scalp.

A solution to this problem would be may be readily available and accessible on the Internet. The advantage of electronic over paper-based information resources is the convenience of access and the efficiency of the search and retrieval capability. Numerous health and medical information sites are available on the Internet and several can

be of tremendous value to the practicing clinician. Sometimes a general Internet search can retrieve useful information that can be evaluated for use on a case-by-case basis. Considering the above scenario one could use an Internet search engine such as altavista (<http://www.altavista.com>) and key in the search term "human bot" or "human bot fly" in quotation marks. A rapid visual scan of the approximately 70 "hits" (as of July 2000) reveals a link to the University of Missouri College of Veterinary Medicine (<http://web.missouri.edu/~vmicrorc/Arthropods/Diptera/Dermatob.htm>). (46) Upon accessing the link you find a page which outlines the taxonomic classification, host spectrum, geographic distribution, morphology, life cycle, sites of infection, pathogenesis, clinical signs, diagnosis, treatment, and public health significance of the Human Bot Fly. The treatment options for humans are documented as being surgical removal or topical application of 1% trichlorfon.

To investigate the status and availability of trichlorfon in Canada you can search the Health Canada Drug Product Database (<http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/dpd.html>). Entering "trichlorfon" into the search module for active ingredients you quickly discover that the product is available as a veterinary paste and thus is not likely to be stocked at a local pharmacy nor is it likely to be labeled for human use. This information can be obtained in minutes using current Internet resources.

Some authors have proposed that creating a personal "Internet library" can augment your information resources. (47) An Internet library can be as simple as a list of links to valid and reliable Internet resources bookmarked on your Internet browser. Alternatively, with the availability of free website hosting sites and free website authoring software it may be more convenient to create a web page devoted to meeting your clinical and other professional practice information needs. An example of an Internet library developed to augment the authors (RMB) critical care practice can be viewed at <http://myinforx.homestead.com>. The advantage of the Internet library web page approach is that your menu of Internet resources can be accessed from any computer with Internet accessibility.

Using the Internet to Keep up with Literature: Effective Browsing

A large volume of new drug information is being published on a continuous basis. Much of this literature; however, will not fundamentally change clinical practice. As any clinical pharmacist knows, staying current with the developments in any field of practice can be difficult. Your practice may require that you stay current with publications that may not be readily accessible.

Information technology can provide a solution to this problem. Email is a tremendous way of effectively browsing the literature for information that may alter or supplement your practice. Many journals now have a feature referred to as an e-mailed table of contents (ETOC). Clinicians can access the homepages of journals that are relevant to their practice areas, subscribe to the ETOC service provided by the publishers and expect to have the journal index delivered by e-mail (often before the library even receives the hardcopy of the issue). If the clinician uses the filtering features available on most e-mail software, they will be able to file these notifications in a specific email folder for future access. Most email programs incorporate search engines and this also permits the clinician to conduct a table of contents search within their own email records. In some cases free or subscriber limited full text access to articles of interest can also be downloaded and added to a local electronic filing system. Full text access to many clinical journals is now becoming available through hospital and University libraries. Pharmacy colleges and associations should be encouraged to provide this service to members.

Workload Prioritization

Pharmacy managers may encounter situations in which there are too few pharmacists to provide a high level of pharmaceutical care to all patients in a particular clinical area. Some pharmacists may therefore be responsible for

providing services to multiple hospital wards. Time and resource limitations make it prohibitive to review all patients. Consequently, pharmacists may be spending a significant portion of their time locating and prioritizing patients who would most likely benefit from having a pharmacist involved in their care. Clinicians need to prioritize patients to ensure that those who are in greatest need receive immediate attention. Typically, those patients at greatest risk of drug-related problems are the elderly, those receiving multiple drugs or drugs with a narrow therapeutic index, and patients with compromised organ function that can be expected to alter drug disposition. Identifying such patients may necessitate reviewing data from a number of different sources such as a ward census lists, laboratory indicators of organ function, and drug profiles. This approach may require time consuming manual assimilation of these data. Time spent prioritizing work reduces the amount of time that clinicians have available to provide patient care.

Information technology applied to workload prioritization can help pharmacists make more time available for direct patient care activities. In collaboration with a hospital information system programmer, the pharmacy department at the Royal Columbian Hospital (RCH) in New Westminster, British Columbia, has developed a computer generated clinical work list (Figure 2). This work list assimilates data from the admissions, pharmacy, nursing, and laboratory modules of the hospital information system and presents these data as information in a format that is useful for the clinician. The work list can be extracted from the hospital system on a ward specific basis according to the needs of the pharmacist providing services to the area. Currently the work list aids in prioritizing patient care activities by outlining key patient features that may be markers of drug related problem risk. In addition to demographic and diagnostic identifiers, the work list includes; patient allergy status, a partial medication profile of target drugs, serum creatinine, calculated creatinine clearance values, and all drug level and coagulation assay results. Historical information dating back 5 days can be included on the list.

The work list can also include pharmacy consult notifications, such as patient teaching requests, ordered by ward. In its current form the worksheet provides a useful way of scanning a large number of patients in order to identify those patients who may be most in need of pharmaceutical care. Also, the work list is used as a passive means of workload measurement. We are currently working on expanding this tool to include nutrition support data, decision support information such as drug dosing guidelines for renal impairment, documentation of pharmacists assessments and two-way synchronization with palm computing devices.

Figure 2. Royal Columbian Hospital Pharmacy Clinical Work List (patient identifiers have been removed).

RUN DATE: 16/05/00 RUN TIME: 1638 RUN USER:		*LIVE* PHARMACY Pharmacy Clinical Worksheet										PAGE					
Unit: HICU		Run Date: 16/05/00															
HICU-1 4		Age: 91 Sex: M Diagnosis: RUPTURED ABDOMINAL AORTIC ANEURYSM Ht: Wt: Admit Date: 12/05/00										Comments					
Allergies: PENICILLIN																	
COLL DATE	COLL TIME	CRCL	CR	DIG	PROCN	NAPA	QUIN	PHENO	CARB	DIL	ALB	LI	VALP	THEO	CSA	PTT	INR
12/05/00	2257	23.4	188														
12/05/00	2257																1.9
12/05/00	2355	23.7	185														
12/05/00	2355															47	1.9
13/05/00	0240	22.0	200														
13/05/00	0600	21.0	209														
13/05/00	0945	19.8	221														
13/05/00	1400	19.4	226														
14/05/00	0600	19.7	223														
14/05/00	1200	19.8	222														
*15/05/00	0545	18.6	236														
*16/05/00	0300															102	
*16/05/00	0700	15.8	277														
*16/05/00	1105															60	
HICU-1 5		Age: 23 Sex: M Diagnosis: MVA-HEAD INJURY Ht: Wt: Admit Date: 13/05/00										Comments					
Allergies: NO KNOWN DRUG ALLERGIES																	
HICU-1 6		Age: 77 Sex: F Diagnosis: POSTOP HERNIA REPAIR, CHRONIC RENAL FAILURE Ht: Wt: Admit Date: 12/05/00										Comments					
Allergies: CODEINE																	
Start : 13/05/00 IMIPENEM 500 MG Stop : 19/05/00 500 MG (1 VIAL) IV Q12H																	
COLL DATE	COLL TIME	--- GENTAMICIN ---			--- VANCOMYCIN ---			--- TOBRAMICIN ---									
		PRE	POST	RAND	PRE	POST	RAND	PRE	POST	RAND							
*16/05/00	0700										11.7						
COLL DATE	COLL TIME	CRCL	CR	DIG	PROCN	NAPA	QUIN	PHENO	CARB	DIL	ALB	LI	VALP	THEO	CSA	PTT	INR
12/05/00	0955	10.9	438														
12/05/00	1850	24.1	199														
12/05/00	2238	23.2	207														
13/05/00	0635	19.8	243														
13/05/00	0635																1.8
14/05/00	0645	14.0	341														

* Indicates new information since previous compilation of work list, ALB = serum albumin, CARB = carbamazepine, Coll= collection CR=serum creatinine, CRCL=creatinine clearance CSA = cyclosporin, DIG = digoxin, DIL=phenytoin, HICU = Intensive Care Unit , Ht = height, INR = international normalized ratio, LI= lithium, NAPA = N-acetyl procainamide, PHENO = phenobarbital, PROCN = procainamide, PTT = partial thromboplastin time, Quin = quinidine, , Rand = random, THEO = theophylline, VALP = valproic acid, Wt = weight.

Integrating Palm-top Technology into the Pharmaceutical Care Process

Monitoring forms are prevalent in pharmacy practice but have some inherent problems. These problems include data redundancy where information already be available in electronic format in the hospital computer system requires manual transcription onto the monitoring form. Other problems are that data on paper forms cannot be automatically sorted, analyzed or retrieved according to user defined criteria, and information transfer is difficult. Often pharmacists are required to document their patient care interventions and tabulate certain indicators for

review. One such intervention that pharmacists are required to document at RCH are cost savings. This refers to any drug cost savings that may result when a pharmacist makes a pharmacotherapy recommendation such as a dose adjustment for renal failure or an alternative antibiotic regimen. Tabulation of cost savings, or clinical outcome indicators, from paper monitoring forms can be cumbersome.

Personal digital assistants (PDAs) can provide a solution to some of the problems inherent to the paper-based monitoring form. Personal digital assistants are hand-held portable computing tools. These devices are becoming ubiquitous in the business world and are making some inroads into the health care sector. (48) Some key capabilities of the PDA include web access, communication, and form development for data management. At RCH we are in the process of integrating palm-top computing technology into the pharmaceutical care process for patients in the intensive care unit. With inexpensive and widely available software, traditional paper monitoring forms can be replicated in electronic format. We are using an electronic palm-top template for the pharmacist work-up of drug therapy, identification of drug related problems, point of care capture and calculation of cost saving drug therapy recommendations with automatic exporting of the information to a spreadsheet for review (Figure 3). (49) We are expanding our efforts to encompass automating the transfer of targeted patient data from the hospital computer system to the PDA.

Figure 3. PDA electronic patient monitoring template and cost savings report

DRPs-ICU Linked

Name	Problem
Doe, John	Risk thromboembolism
Doe, John	Dose adjustment in RF

Filters Find Again Done New Sort

ICU Cost Savings Fiscal Period 4

Date	Drug	Dose	Route	Sig	Intervention	NewDrug	NewDose	NewRoute	NewSig	\$/mg/dose	Atkoses saved	cost savings
02/03/2000	Amiodarone	600	IV	Q04h	Decr dose	No Value	300	No Value	Q04h	100	5	\$300.00
02/03/2000	Cefepime	2g	IV	Q12h	Alt Drug	Cefuroxime	1500mg	IV	Q0h	200	1	\$200.00
02/03/2000	Metronidazole	500mg	IV	Q12h	D/C	No Value	No Value	No Value	No Value	134	10	\$13.40
01/06/2000	Ezetimibe	30	SC	Q12h	Alt Drug	Heprin	3000a	SC	Q12h	5	10	\$50.00
02/03/2000	Metronidazole	1g	IV	Q12h	D/C	No Value	No Value	No Value	No Value	21.2	18	\$381.60
02/03/2000	Insiprem	400mg	IV	Q0h	D/C	No Value	No Value	No Value	No Value	12	15	\$180.00
17/01/2000	Insiprem	1g	IV	Q12h	D/C	No Value	No Value	No Value	No Value	2.2	10	\$22.00
17/02/2000	Insiprem	400mg	IV	Q0h	Extrenal route	Insiprem	400mg	Extrenal route	Q12h	2.2	10	\$44.00
17/02/2000	Insiprem	400mg	IV	Q0h	D/C	No Value	No Value	No Value	No Value	24	5	\$120.00
18/01/2000	Metronidazole	500mg	IV	Q12h	D/C	No Value	No Value	No Value	No Value	134	10	\$13.40
19/01/2000	Metronidazole	500mg	IV	Q04h	D/C	No Value	No Value	No Value	No Value	250	3	\$750.00
21/02/2000	Insiprem	400mg	IV	Q0h	D/C	No Value	No Value	No Value	No Value	12	15	\$180.00
21/02/2000	Cipro	400mg	IV	Q04h	Extrenal route	No Value	400mg	Extrenal route	Q12h	30	10	\$300.00
22/02/2000	Insiprem	400mg	IV	Q0h	D/C	No Value	No Value	No Value	No Value	12	20	\$240.00
22/02/2000	Cipro	400mg	IV	Q12h	D/C	No Value	No Value	No Value	No Value	33	10	\$330.00
31/01/2000	Cipro	400mg	IV	Q04h	Extrenal route	No Value	250mg	No Value	No Value	29	4	\$116.00
31/01/2000	Fluconazole	400mg	IV	Q04h	Extrenal route	No Value	400mg	No Value	No Value	30	2	\$100.00
Total Savings												\$4,002.20

Potential Shortcomings and Limitations of Current Information Technology

Although information technology can provide many benefits in clinical practice, clinicians need to be aware of some of the negative aspects of the state of this technology today. Probably the single greatest problem facing clinicians practicing in a health care facility is the lack of standardization within and across institutions. Many hospitals use multiple independent databases (e.g. pharmacy, laboratory, radiology) that are poorly integrated and result in an inability to combine patient information from various sources into a meaningful record. For example, the system in use at RCH only recently involved distinct computer hardware vendors and operating systems for the laboratory

and pharmacy systems. One hardware vendor eventually combined these systems but even then each module, laboratory and pharmacy, concurrently functioned under separate operating systems. In addition, the operating system had limited ability to share data. This system complexity necessitated the involvement of a programmer in order to generate the daily clinical pharmacist work list described above. Incomplete information can result when data that a customized hospital program requires is moved, or given another internal reference, from one part of a non-integrated hospital system to another. We experienced this difficulty when the laboratory changed the coding system for some drug assay samples to better meet the needs of the laboratory. In this case certain drug level assay results were not captured by the RCH clinical work list described above. A corporate decision to change hardware or software vendors could suddenly render such customized efforts non-available.

Over dependence on technology can be a drawback and computers cannot do the job that is required of the pharmacist. Technology aids us in the acquisition, sorting, and formatting of data into information yet the clinician still must analyze the data, make an assessment and formulate a plan. There is a limit to how much information can be presented to the human mind for interpretation. The technology if not monitored and applied appropriately can provide too much data and this can worsen the information overload that many practitioners may feel. These potential negative aspects of information technology need to be considered, as computer resources are integrated into practice.

Getting Started

Getting started with integrating computer resources into your clinical practice need not be onerous. Computer literacy from an end user perspective is the fundamental starting point. File management techniques for storing and accessing your information are necessary. Internet connectivity and e-mail ability is required in order to draw upon the clinical resources available on the Internet. Take advantage of software tutorials and course offerings, as they become available in your community or institution. If you do not have Internet connectivity from your practice area consider implementing some of the free services that are available. Free Internet connectivity via modem is available to some geographical areas through AltaVista <http://www.altavista.com> or Excite <http://www.excite.com> and alternatives for free e-mail are numerous. For a free e-mail account combined with on-line free file storage space visit <http://www.visto.com>. You may find that the palm-computing platform can be of value to your practice for both patient monitoring and as a portable reference or resource station. Examine <http://www.pdamd.com> or <http://www.healthypalmpilot.com> for examples of clinical applications for these devices. A step by step integration of technology targeted at solving an existing problem or improving an existing process could be a tremendous benefit to you.

Summary

The evidence-based practice paradigm has increased the information needs of the clinician to such an extent that it is simply unmanageable by traditional paper-based methods. Progress in communications and computing technology has lead to the evolvement of medical informatics as a new discipline of study for all health professionals. With proper instruction or simple guidance, clinicians can incorporate informatics tools into their daily practice to improve the way in which they harness data and manage information. The modern pharmacist must be competent in specific computer skills to collect, store, retrieve and send drug and patient related data for administrative and clinical applications in practice. Basic computer literacy combined with a targeted use of existing software and Internet resources can help accomplish these goals.

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Appendix I. Informatics Websites of Interest

1. The Informatics Review (<http://www.informatics-review.com>)

This is an electronic serial designed to allow medical and information system professionals interested in the latest academic developments in clinical informatics and computing to stay abreast of this rapidly evolving field.

2. **International Journal of Medical Informatics** (<http://www.elsevier.co.jp/inca/publications/store/5/0/6/0/4/0/>)

This journal disseminates original results and interpretative reviews concerning the field of medical informatics.

3. **Journal of the American Medical Informatics Association** (<http://www.jamia.org>)

This is a bimonthly journal presenting peer-reviewed articles for assisting physicians, informaticians, scientists, nurses, and other health care professionals in developing and applying medical informatics to patient care, teaching, research, and health care administration.

4. **MD Computing** (<http://www.mdcomputing.com>)

Another bimonthly publication that provides information on the use and application of computers and computer technology in medicine and healthcare systems. *MD Computing* is written for medical and other healthcare professionals who are involved in the research and development of medical and healthcare information systems as well as those in medical education and practice.

5. **The Handbook of Medical informatics** (http://www.mieur.nl/mihandbook/r_3_3/handbook/home.htm)

This is an on-line handbook providing a systematic overview of medical informatics for health care professionals computer scientists and students.

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Medical Informatics: Pharmacists' Needs and Applications in Clinical Practice

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Pharmacy is an information intensive profession. The information explosion and the emphasis on evidence-based medicine are forcing changes in pharmacists' roles. Affordable computers combined with the advancement of information technology can now provide extremely useful clinical applications for pharmacists in their own working conditions. Computers can enhance practice by providing a rapid and effective means of accessing, retrieving, analyzing, sharing and storing large volumes of information pertinent to patient care. Several examples of the effective use of informatics tools in a hospital intensive care unit are presented such as: rapidly retrieving information to solve an urgent case; creating a personal Internet library, efficiently browsing the Internet, using computerized patient care worksheets and integrating hand-held portable computing tools into the pharmaceutical care process. These examples can be applied to any practice setting. Informatics is an emerging academic discipline in the health sciences. Essential informatics skills for pharmacists are reviewed. We describe a proposed medical informatics syllabus for the clinical pharmacist to provide the knowledge and skills in informatics essential for today's practice.

J Inform Pharmacother 2000;2:306-318.

Pharmacy is an information intensive profession that demands effective use of technology to manage an ever-expanding body of knowledge. "Information anxiety" is described as the frustration of being inundated by an overabundance of information sources while being unable to navigate them to find specific needed information. (1) In order to minimize information anxiety, pharmacists must be competent in the use of computers to collect; store, retrieve and send drug and patient related data for both administrative and clinical purposes. The importance of information technology to the future of pharmacy

practice has been well described in the literature. (2-5) Information technology has always influenced pharmacy practice, but now with the availability of inexpensive yet powerful computers, and rapid communication via the Internet and other networks, this technology will exert an increasing force in changing roles for pharmacists. An understanding of some information technology principles may help practitioners avoid being "buried alive" in the streams of data that now permeate the health care setting. (6)

The term *medical informatics* has been defined as "the field concerned with the cognitive, information processing, and communication tasks of medical practice, education, and research, including the information science and technology to support these tasks." (1) The informatics field also includes advanced research initiatives that can be used in clinical practice including: i) expert clinical decision analysis and decision support initiatives (7-11); ii) electronic medical records (12); iii) data warehousing and analysis of collaborative data sets (13,14); iv) computer automated drug interaction, adverse drug reaction and drug usage monitoring systems (15-17) and; v) telecommunication advances such as video conferencing via Internet and intranet connected systems. (2) Advancements in hospital decision support systems and electronic medical records have been slow and are not as yet widely used as these systems have been more difficult to implement than previously anticipated. (2,18) There are; however, currently available off-the-shelf technologies that can be utilized by individual clinical practitioners. It would be prudent for all clinicians to familiarize themselves with these resources and learn how to apply them to their practice in a practical fashion. Primers on Internet use and online clinical resource utilization regularly appear in the medical literature. (19,20)

Pharmacists need to develop a set of practical

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informatics skills to manage the data and information challenges in their practice. This article focuses on some available computer resources that can augment clinical practice. Informatics skills considered essential for pharmacists to learn and examples of how these skills apply to clinical practice are provided.

Essential Informations Skills for Pharmacists

The evidence-based practice paradigm increases clinician information needs and to meet these needs, clinicians require rapid access to resources that provide content that is relevant, valid, and can be obtained with minimal effort. (21) Ideal information resources are electronic, portable, connected to valid databases and servant to the user. (21-23) While pharmacists may not need to be experts in information systems, they do need sophisticated end-user knowledge of technologies that are available and applicable to research and clinical practice. These technologies include personal and network computing; hospital information systems; personal digital assistants; the Internet; word processing; and presentation, statistical analysis and database management software. Those practitioners who do not incorporate some of these tools into their practice will undoubtedly have difficulty keeping up with the clinical information necessary for evidence-based practice. As other health care professionals continue to incorporate available technology into their practices, pharmacists need to advance at least as quickly to ensure that they are at the forefront of this movement. Only by doing so will they be able to ensure that they continue to be the drug expert in the health care team. The development of automated drug dispensing, clinical monitoring and clinical decision support systems is evolving rapidly and these developments challenge the pharmacist to maintain an evidence-based and patient-centered role in the healthcare system.

Essential clinical informatics skills have previously been identified from a medical perspective. (24) Coiera proposes that, in addition to having basic computer skills, ten essential clinical informatics skills are needed in order for clinicians to properly manage information (Table 1).

Upon reviewing the American College of Clinical Pharmacy position statement describing the practice guidelines for a pharmacotherapeutic specialist, one could infer that many of these same skills are integral to pharmacy practice. (25) It is clear that effective information management requires more than basic computer literacy. Computer skills are fundamental to integrating technology and clinical practice and to facilitating the effective transformation of data to useable clinical information.

Student and Clinicians Needs for Informatics Training

Medical Informatics is fervently being addressed as an emerging academic discipline in medicine, nursing and dentistry. (1,26,27) Many medical schools and residency programs are including informatics training in their programs. (28-33) Dentistry schools likewise consider informatics essential in their training. (34,35) Nursing has developed informatics to the point of debating "nursing informatics" as a distinct discipline. (36-40) Pharmacy is certainly one of the most information-intensive professions and yet we have not taken the lead in developing informatics specific for our needs and where medicine and nursing needs overlap ours. Currently there is a lack of research addressing informatics needs in any area of pharmacy practice and pharmacy education.

Certainly anxiety is produced by the continuous statements that health care technology will change the role of pharmacists and create expanded opportunities for pharmacists in the future. Unfortunately such statements about future capabilities of technological advances do nothing to aid in defining what the roles will be or how to get there from our present state. Now that computer equipment has finally reached a stage of being affordable, user friendly, and that evidenced-based information is readily available and easily accessed via the world wide web, we felt it was urgent to develop an informatics course for undergraduate pharmacy students. While a number of organizations have developed recommendations for medical informatics education, none are directed specifically for pharmacists needs. (41-44) Upon accepting the reality that health care technology is in a state of rapid transition, we attempted to design an essential informatics knowledge and skills course for a clinical

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Table 1: Ten Essential Clinical Informatics Skills (24)

1. Understand the dynamic and uncertain nature of medical knowledge and know how to keep personal knowledge and skills up-to-date.
 2. Search for and assess knowledge according to the statistical basis of scientific evidence.
 3. Understand some of the logical and statistical models of the diagnostic process.
 4. Interpret uncertain clinical data and deal with artifact and error.
 5. Analyze and structure clinical decisions in terms of risks and benefits.
 6. Adapt and apply clinical knowledge to the individual circumstances of patients.
 7. Access, assess, select and apply a treatment guideline; adapt it to local circumstances; and communicate and record variations in treatment plan and outcome.
 8. Structure and record clinical data in a form appropriate for the immediate clinical task, for communication with colleagues, or for epidemiological purposes.
 9. Select and utilize the most appropriate communication method for a given task (e.g. face-to-face conversation, telephone, e-mail, video, voice-mail, letter).
 10. Structure and communicate messages in a manner most suited to the recipient, task and chosen communication medium.
-

pharmacy practitioner today. The central guiding question was how could computers be used to make the clinical pharmacists' role easier yet more effective in improving patient care? The overall goals of the course that we propose are: 1) to develop an awareness of the usefulness and limitations of computers and informatics tools in pharmacy practice; 2) to demonstrate and facilitate the development of essential skills for the use of technology to meet the increasing and evolving demands of pharmacy practice today; 3) to provide a framework for life-long technology-assisted continuing education and clinical practice; and 4) to develop an appreciation of the impact of automation on pharmacy practice. Our proposed syllabus includes computer literacy, and software applications; communication via the Internet; pharmacy automation; and information management. Throughout the development of this syllabus we attempted to prioritize topics that are applicable in practice today and yet remain comprehensive in the variety of informatics topics addressed.

Currently there exists great interest in learning about informatics. This was revealed in a recent continuing educational needs survey of 2,500 Canadian physicians in general or family practice. (45) This survey revealed that almost 55% of respondents selected informatics and computers over other

professional or clinical options as the highest priority topic for improvement in knowledge and skills. Interestingly, 63% of respondents indicated that they had no access to computer support for practice. This confirms our experience that there is a recognized interest in informatics training. Over the past year, we have had many requests from pharmacy students, faculty, pharmacists and family physicians to be taught informatics skills. Consequently we have given separate presentations encompassing introductory applied informatics material for both pharmacy students and family physicians in both university-based and hospital-based computer labs. These sessions have resulted in numerous requests for additional training topics. Based upon our personal experience, the perception that the majority of health professionals has access to and use information readily available through computers is not a reality. The challenge of educating future and current health professionals in informatics must be addressed now.

Examples of the Effective Use of Informatics Tools in Everyday Practice

Here are some practical examples how readily

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available computer hardware and software can be integrated into every day clinical practice.

Rapid Retrieval of Drug Information

You are in the Intensive Care Unit preparing for morning interdisciplinary rounds. The patient just admitted to Bed-1 is a 38-year-old female with septic shock secondary to bacteremia. The patient has multiple loculated hepatic abscesses and is receiving high doses of inotropic drugs. Fluid balance has been optimized and she is maintaining a mean arterial pressure of 55 mmHg with a regimen of dopamine 20 mcg/kg/min and norepinephrine 20 mcg/min. You have been keeping up with the critical care literature and realize that a viable therapeutic alternative for pressor support in this patient may be a vasopressin infusion. Rounds start in 5 minutes and you can't remember the dosing protocol nor the specific inclusion criteria reported for the studied patient population. You know that you have the relevant papers in your "files" somewhere but locating them will likely take some time.

This is a common scenario for all practicing clinicians who need to have rapid access to previously retrieved reference material that is now located personal library files. One potential solution to this problem is to create your own digital library that is portable and readily accessible. Resources are available to electronically file publications. Many journals are now available on-line with full text access to personal and institutional subscribers. Journal articles that are not available online can be converted to electronic format with a scanning device and the appropriate file storage software. Key articles can be made readily retrievable by electronically filing the digital version on your computer or a network hard drive. A common format for digital document distribution is the portable document format ("PDF") that has been created by Adobe Systems Inc. (<http://www.adobe.com>). Portable document format files can be read by anyone who has installed the free reader software. These files can be stored locally and organized in a directory structure that is logical to the user such as a head-to-toe systems approach. Adding relevant PDF format journal articles takes seconds with basic file management techniques. The advantage of having your personal reference files stored digitally is that

you can quickly access the files from your PC or any networked PC in your hospital.

Revisiting the above case scenario, 5 minutes is ample time to log on to a networked PC, locate and retrieve your relevant files pertaining to the use of vasopressin for septic shock and be prepared for a bedside discussion about the possibility of instituting this mode of therapy. Occasionally it may be difficult to recall the folder in which the file is located. In such cases, the "find file or folder" function of your computer operating system can be used to search your references by file name. This will provide you with a list of the relevant files on your computer. Some third party file indexing software can be used to search your files by key words throughout the text of the document. An example of the authors (RMB) networked electronic library pertaining to the above case scenario is outlined in Figure 1. Once located, the relevant paper can be printed or viewed on screen.

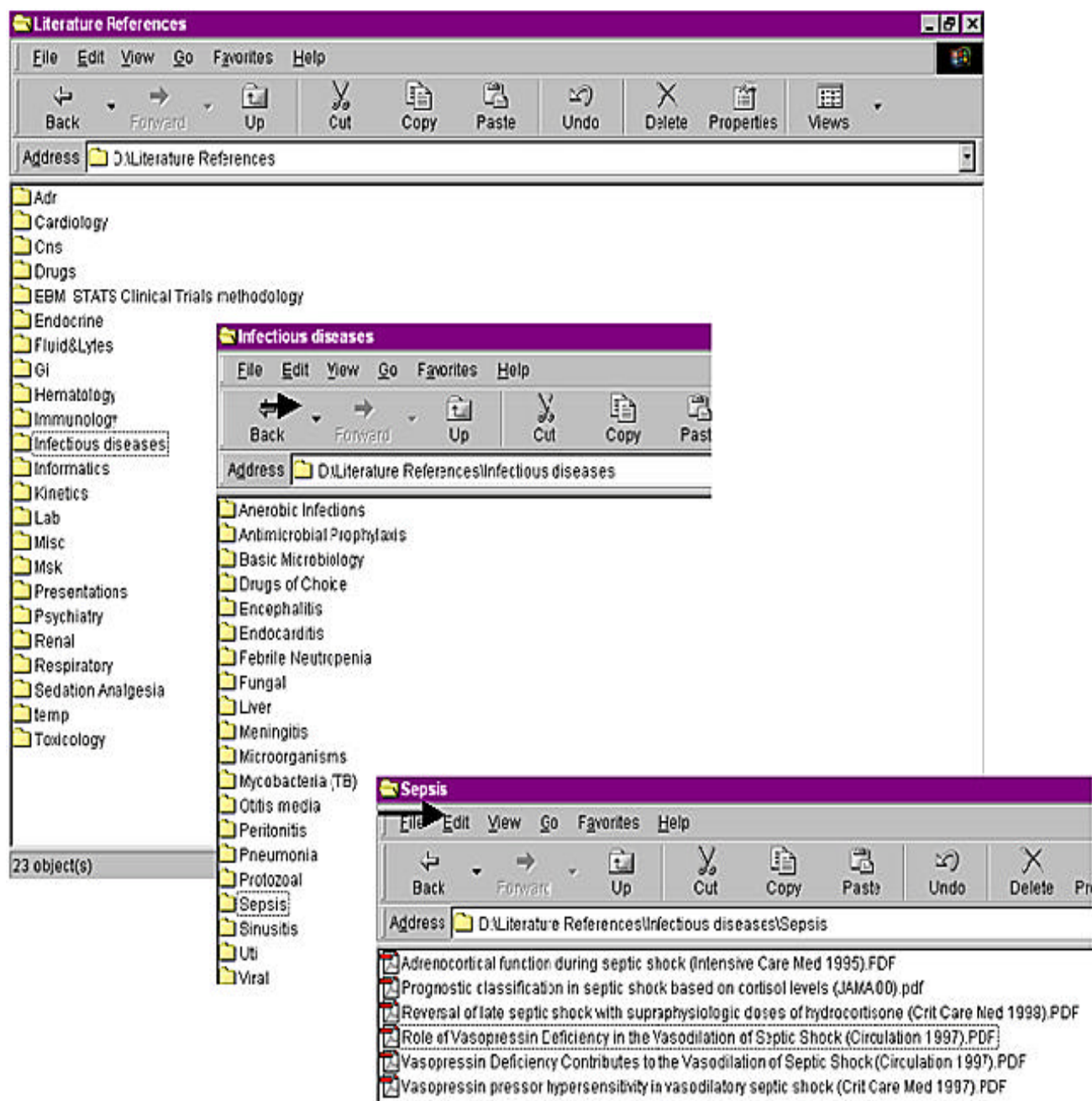
Integrating on-Line Resources into your Daily Practice

A family physician calls you asking about pharmacotherapeutic options to assist in removing a Bot Fly that is embedded in a patients scalp. The patient is a 40-year-old botanist who was contracted to do some work on a farm in Central America. Upon returning home she was noted to have a swollen 2 cm diameter itchy boil-like erythematous area on top of her head. Being familiar with the parasite hazards in Central America and having experienced Bot Fly problems in the past, the patient was suspicious about this itchy area on her scalp.

A solution to this problem would be readily available and accessible on the Internet. The advantage of electronic over paper-based information resources is the convenience of access and the efficiency of the search and retrieval capability. Numerous health and medical information sites are available on the Internet and several can be of tremendous value to the practicing clinician. Sometimes a general Internet search can retrieve useful information that can be evaluated for use on a case-by-case basis. Considering the above scenario one could use an Internet search engine such as altavista (<http://www.altavista.com>) and key in the

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Figure 1. Directory structure of a digital reference library on a personal computer



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search term "human bot" or "human bot fly" in quotation marks. A rapid visual scan of the approximately 70 "hits" (as of July 2000) reveals a link to the University of Missouri College of Veterinary Medicine

(<http://web.missouri.edu/~vmicrorc/Arthropods/Diptera/Dermatob.htm>). (46) Upon accessing the link you find a page which outlines the taxonomic classification, host spectrum, geographic distribution, morphology, life cycle, sites of infection, pathogenesis, clinical signs, diagnosis, treatment, and public health significance of the Human Bot Fly. The treatment options for humans are documented as being surgical removal or topical application of 1% trichlorfon.

To investigate the status and availability of trichlorfon in Canada you can search the Health Canada Drug Product Database (<http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/dpd.html>). Entering "trichlorfon" into the search module for active ingredients you quickly discover that the product is available as a veterinary paste and thus is not likely to be stocked at a local pharmacy nor is it likely to be labeled for human use. This information can be obtained in minutes using current Internet resources.

Some authors have proposed that creating a personal "Internet library" can augment your information resources. (47) An Internet library can be as simple as a list of links to valid and reliable Internet resources bookmarked on your Internet browser. Alternatively, with the availability of free website hosting sites and free website authoring software it may be more convenient to create a web page devoted to meeting your clinical and other professional practice information needs. An example of an Internet library developed to augment the authors (RMB) critical care practice can be viewed at <http://myinforx.homestead.com>. The advantage of the Internet library web page approach is that your menu of Internet resources can be accessed from any computer with Internet accessibility.

Using the Internet to Keep up with Literature: Effective Browsing

A large volume of new drug information is being published on a continuous basis. Much of this

literature; however, will not fundamentally change clinical practice. As any clinical pharmacist knows, staying current with the developments in any field of practice can be difficult. Your practice may require that you stay current with publications that may not be readily accessible.

Information technology can provide a solution to this problem. Email is a tremendous way of effectively browsing the literature for information that may alter or supplement your practice. Many journals now have a feature referred to as an e-mailed table of contents (ETOC). Clinicians can access the homepages of journals that are relevant to their practice areas, subscribe to the ETOC service provided by the publishers and expect to have the journal index delivered by e-mail (often before the library even receives the hardcopy of the issue). If the clinician uses the filtering features available on most e-mail software, they will be able to file these notifications in a specific email folder for future access. Most email programs incorporate search engines and this also permits the clinician to conduct a table of contents search within their own email records. In some cases free or subscriber limited full text access to articles of interest can also be downloaded and added to a local electronic filing system. Full text access to many clinical journals is now becoming available through hospital and University libraries. Pharmacy colleges and associations should be encouraged to provide this service to members.

Workload Prioritization

Pharmacy managers may encounter situations in which there are too few pharmacists to provide a high level of pharmaceutical care to all patients in a particular clinical area. Some pharmacists may therefore be responsible for providing services to multiple hospital wards. Time and resource limitations make it prohibitive to review all patients. Consequently, pharmacists may be spending a significant portion of their time locating and prioritizing patients who would most likely benefit from having a pharmacist involved in their care. Clinicians need to prioritize patients to ensure that those who are in greatest need receive immediate attention. Typically, those patients at greatest risk of drug-related problems are the elderly, those receiving

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multiple drugs or drugs with a narrow therapeutic index, and patients with compromised organ function that can be expected to alter drug disposition. Identifying such patients may necessitate reviewing data from a number of different sources such as a ward census lists, laboratory indicators of organ function, and drug profiles. This approach may require time consuming manual assimilation of these data. Time spent prioritizing work reduces the amount of time that clinicians have available to provide patient care.

Information technology applied to workload prioritization can help pharmacists make more time available for direct patient care activities. In collaboration with a hospital information system programmer, the pharmacy department at the Royal Columbian Hospital (RCH) in New Westminster, British Columbia, has developed a computer generated clinical work list (Figure 2). This work list assimilates data from the admissions, pharmacy, nursing, and laboratory modules of the hospital information system and presents these data as information in a format that is useful for the clinician. The work list can be extracted from the hospital system on a ward specific basis according to the needs of the pharmacist providing services to the area. Currently the work list aids in prioritizing patient care activities by outlining key patient features that may be markers of drug related problem risk. In addition to demographic and diagnostic identifiers, the work list includes; patient allergy status, a partial medication profile of target drugs, serum creatinine, calculated creatinine clearance values, and all drug level and coagulation assay results. Historical information dating back 5 days can be included on the list.

The work list can also include pharmacy consult notifications, such as patient teaching requests, ordered by ward. In its current form the worksheet provides a useful way of scanning a large number of patients in order to identify those patients who may be most in need of pharmaceutical care. Also, the work list is used as a passive means of workload measurement. We are currently working on expanding this tool to include nutrition support data, decision support information such as drug dosing guidelines for renal impairment, documentation of pharmacists assessments and two-way synchronization with palm computing devices.

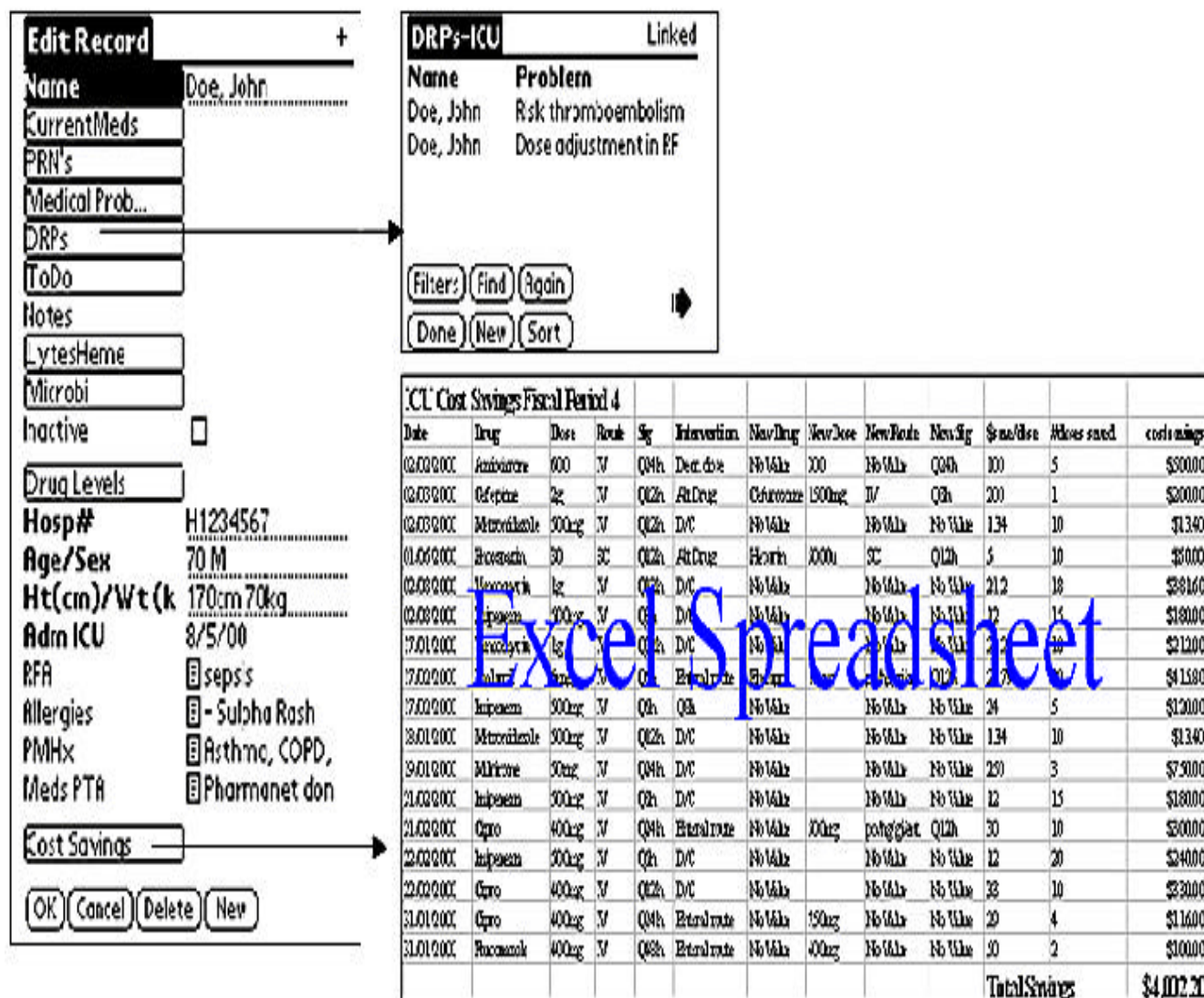
Integrating Palm-top Technology into the Pharmaceutical Care Process

Monitoring forms are prevalent in pharmacy practice but have some inherent problems. These problems include data redundancy where information already be available in electronic format in the hospital computer system requires manual transcription onto the monitoring form. Other problems are that data on paper forms cannot be automatically sorted, analyzed or retrieved according to user defined criteria, and information transfer is difficult. Often pharmacists are required to document their patient care interventions and tabulate certain indicators for review. One such intervention that pharmacists are required to document at RCH are cost savings. This refers to any drug cost savings that may result when a pharmacist makes a pharmacotherapy recommendation such as a dose adjustment for renal failure or an alternative antibiotic regimen. Tabulation of cost savings, or clinical outcome indicators, from paper monitoring forms can be cumbersome.

Personal digital assistants (PDAs) can provide a solution to some of the problems inherent to the paper-based monitoring form. Personal digital assistants are hand-held portable computing tools. These devices are becoming ubiquitous in the business world and are making some inroads into the health care sector. (48) Some key capabilities of the PDA include web access, communication, and form development for data management. At RCH we are in the process of integrating palm-top computing technology into the pharmaceutical care process for patients in the intensive care unit. With inexpensive and widely available software, traditional paper monitoring forms can be replicated in electronic format. We are using an electronic palm-top template for the pharmacist work-up of drug therapy, identification of drug related problems, point of care capture and calculation of cost saving drug therapy recommendations with automatic exporting of the information to a spreadsheet for review (Figure 3). (49) We are expanding our efforts to encompass automating the transfer of targeted patient data from the hospital computer system to the PDA.

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Figure 3. PDA electronic patient monitoring template and cost savings report



Potential Shortcomings and Limitations of Current Information Technology

Although information technology can provide many benefits in clinical practice, clinicians need to be aware of some of the negative aspects of the state of this technology today. Probably the single greatest problem facing clinicians practicing in a health care facility is the lack of standardization within and across institutions. Many hospitals use multiple independent

databases (e.g. pharmacy, laboratory, radiology) that are poorly integrated and result in an inability to combine patient information from various sources into a meaningful record. For example, the system in use at RCH only recently involved distinct computer hardware vendors and operating systems for the laboratory and pharmacy systems. One hardware vendor eventually combined these systems but even then each module, laboratory and pharmacy, concurrently functioned under separate operating systems. In addition, the operating system had

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limited ability to share data. This system complexity necessitated the involvement of a programmer in order to generate the daily clinical pharmacist work list described above. Incomplete information can result when data that a customized hospital program requires is moved, or given another internal reference, from one part of a non-integrated hospital system to another. We experienced this difficulty when the laboratory changed the coding system for some drug assay samples to better meet the needs of the laboratory. In this case certain drug level assay results were not captured by the RCH clinical work list described above. A corporate decision to change hardware or software vendors could suddenly render such customized efforts non-available.

Over dependence on technology can be a drawback and computers cannot do the job that is required of the pharmacist. Technology aids us in the acquisition, sorting, and formatting of data into information yet the clinician still must analyze the data, make an assessment and formulate a plan. There is a limit to how much information can be presented to the human mind for interpretation. The technology if not monitored and applied appropriately can provide too much data and this can worsen the information overload that many practitioners may feel. These potential negative aspects of information technology need to be considered, as computer resources are integrated into practice.

Getting Started

Getting started with integrating computer resources into your clinical practice need not be onerous. Computer literacy from an end user perspective is the fundamental starting point. File management techniques for storing and accessing your information are necessary. Internet connectivity and e-mail ability is required in order to draw upon the clinical resources available on the Internet. Take advantage of software tutorials and course offerings, as they become available in your community or institution. If you do not have Internet connectivity from your practice area consider implementing some of the free services that are available. Free Internet connectivity via modem is available to some geographical areas through AltaVista <http://www.altavista.com> or Excite <http://www.excite.com> and alternatives for free e-

mail are numerous. For a free e-mail account combined with on-line free file storage space visit <http://www.visto.com>. You may find that the palm-computing platform can be of value to your practice for both patient monitoring and as a portable reference or resource station. Examine <http://www.pdamd.com> or <http://www.healthypalmpilot.com> for examples of clinical applications for these devices. A step-by-step integration of technology targeted at solving an existing problem or improving an existing process could be a tremendous benefit to you.

Summary

The evidence-based practice paradigm has increased the information needs of the clinician to such an extent that it is simply unmanageable by traditional paper-based methods. Progress in communications and computing technology has lead to the evolvement of medical informatics as a new discipline of study for all health professionals. With proper instruction or simple guidance, clinicians can incorporate informatics tools into their daily practice to improve the way in which they harness data and manage information. The modern pharmacist must be competent in specific computer skills to collect, store, retrieve and send drug and patient related data for administrative and clinical applications in practice. Basic computer literacy combined with a targeted use of existing software and Internet resources can help accomplish these goals.

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Appendix Informatics Websites of Interest

1. The Informatics Review

<http://www.informatics-review.com>

This is an electronic serial designed to allow medical and information system professionals interested in the latest academic developments in clinical informatics and computing to stay abreast of this rapidly evolving field.

2. International Journal of Medical Informatics

<http://www.elsevier.co.jp/inca/publications/store/5/0/6/0/4/0/>

This journal disseminates original results and interpretative reviews concerning the field of medical informatics.

3. Journal of the American Medical Informatics Association

<http://www.jamia.org>

This is a bimonthly journal presenting peer-

I.

reviewed articles for assisting physicians, informaticians, scientists, nurses, and other health care professionals in developing and applying medical informatics to patient care, teaching, research, and health care administration.

4. MDComputing

<http://www.mdcomputing.com>

Another bimonthly publication that provides information on the use and application of computers and computer technology in medicine and healthcare systems. *MD Computing* is written for medical and other healthcare professionals who are involved in the research and development of medical and healthcare information systems as well as those in medical education and practice.

5. The Handbook of Medical informatics

http://www.mieur.nl/mihandbook/r_3_3/handbook/home.htm

This is an on-line handbook providing a systematic overview of medical informatics for health care professionals computer scientists and students.

Original Research Article

Stability of Aminophylline in Extemporaneously-Prepared Oral Suspensions

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Abstract

Rationale: Oral aminophylline liquid formulations are not available in Canada. The advent of a commercially-available vehicle (1:1 Ora Sweet:Ora Plus) provides an alternative to extemporaneous compounding, but stability information is unavailable for aminophylline in oral suspensions prepared with this newer vehicle.

Objectives: To evaluate the stability of aminophylline 3 mg/mL (pediatric) and 21 mg/mL (adult) in the Ora Sweet:Ora Plus vehicle, at 4°C and 25°C, over a period of 91 days.

Methods: Triplicate suspensions were prepared in 50 mL amber glass prescription bottles using aminophylline injection 25 mg/mL. For each concentration, six bottles were filled; three were stored at 4°C (refrigerated) and three at 25°C (room temperature). Samples were removed from each bottle initially and at weekly intervals, at which time their physical appearance, odour, and pH were also examined. The samples were stored in a -85°C freezer until batch-analysis by a validated stability-indicating high performance liquid chromatography (HPLC) assay using ultraviolet detection at 254 nm. Percent of initial drug concentration remaining was calculated for each sample. Stability was defined as maintenance of at least 90% of initial drug concentration.

Results: The majority of the opaque white suspensions had a sweet smell and were easily resuspendable; however, the 21 mg/mL suspensions stored at 4°C formed white needle crystals within 7 days. Other than the crystal formation, no significant changes in physical appearance, odour, or pH were observed over the course of the study. The results of the HPLC analysis revealed that the 3 mg/mL suspensions at both temperatures (4°C and 25°C) and the 21 mg/mL suspensions at 25°C maintained at least 90% of their initial concentrations. However, the 21 mg/mL suspensions stored at 4°C failed to maintain 90% of initial concentration.

Conclusions: At the end of 91 days, aminophylline is both chemically and physically stable in 1:1 Ora Sweet:Ora Plus as a 3 mg/mL suspension stored at 4°C and 25°C, and as a 21 mg/mL suspension stored at 25°C. Accordingly, the expiration dates of these specific suspensions can be extended to 90 days.

J Inform Pharmacother 2000;2:100-6.

Introduction

Aminophylline, the ethylenediamine salt equivalent to 79% theophylline, has long been used in pulmonary diseases including asthma, chronic bronchitis, and emphysema. In our hospital, aminophylline is primarily used as a respiratory

stimulant for first-line treatment of apnea of prematurity.(1) Solid oral dosage forms of aminophylline are undesirable in this pediatric population.

While several liquid formulations of aminophylline are marketed in the United States, none are commercially available in Canada.(2,3) Liquid theophylline preparations are available in Canada (e.g. Theolair® liquid (3M), Theophylline elixir (Technilab) and Theophylline solution (Desbergers)(3); however, in some institutions such as ours, these preparations are not used due to concerns about potential excipient-related toxicities.

Commercially-available theophylline solution products contain excipients (e.g., sorbitol, alcohol, propylene glycol) that are inappropriate for the pediatric population, particularly the neonatal and infant age groups. Specifically, Theolair® contains sorbitol which may be associated with gastrointestinal side effects such as osmotic diarrhea and abdominal pain.(4,5) The alcohol content in theophylline elixir combined with the reduced activity of alcohol dehydrogenase in children may result in accumulation and potential acute toxicity until this enzyme system reaches adult levels of activity.(4) Theophylline solutions that contain propylene glycol may put premature infants at risk for displacement of bilirubin and consequently hyperbilirubinemia.(4,5,6). Excessive intake of propylene glycol and subsequent metabolism to lactic acid may also cause the development of hyperosmolality and lactic acidosis.(4,6) Other additives such as flavouring agents and dyes may also be problematic.(4,5,6)

As a result of our reluctance to use commercially available products, we extemporaneously compound oral aminophylline preparations for use in our pediatric patients. To date, our oral aminophylline suspensions have been prepared in a methylcellulose vehicle and given, based on historical procedures, an empirical expiration date of 7 days. The methylcellulose suspensions present some significant problems, including intensive labour, inability by community pharmacists to prepare, short expiration dates and inconvenience to outpatients; all of these factors are expected to lead to increased costs to the health-care system.

A commercially-available vehicle (1:1 mixture of Ora Sweet:Ora Plus (footnote a), a syrup and suspending agent, respectively) has recently emerged as an alternative to methylcellulose. Ora Sweet (footnote a) contains purified water, sucrose, glycerin, sorbitol, and flavoring, with citric acid and sodium phosphate as buffers, and methylparaben and potassium sorbate as preservatives. Ora Plus (footnote a) contains purified water, microcrystalline cellulose, carboxymethylcellulose sodium, xanthan gum, carrageenan, citric acid and sodium phosphate as buffers, simethicone as an antifoaming agent, and methylparaben and potassium sorbate as preservatives. Ora Sweet:Ora Plus has been widely accepted as a suitable vehicle for use in the pediatric population due to the lack of inappropriate additives. Furthermore, this newer vehicle is expected to eliminate many of the disadvantages associated with methylcellulose, since it is reportedly easier to work with and more readily available in the community. However, stability information for aminophylline in Ora Sweet:Ora Plus is not currently available.

Pharmaceutical stability is defined as the extent to which a product retains, within specified limits and throughout its period of storage and use (i.e., shelf-life), the same properties and characteristics that it possessed at the time of manufacture.(7) The types of stability pertinent to our study include chemical and physical stability. Chemical stability refers to the integrity and labeled potency of the active ingredient and physical stability refers to the maintenance of the original physical properties and appearance.

Objective

The objective of the study was to evaluate the stability of aminophylline 3 mg/mL (pediatric) and 21 mg/mL (adult) in oral suspensions, extemporaneously prepared with the Ora Sweet:Ora Plus vehicle at 4°C and 25°C over a period of 91 days.

Methodology

Preparation of oral suspensions

The suspensions were prepared in triplicate using commercially-available aminophylline injection 25 mg/mL (footnote b) in the 1:1 Ora Sweet:Ora Plus vehicle. The 3 mg/mL (pediatric) and 21 mg/mL (adult) concentrations represent those used in clinical practice. For each concentration, six 50 mL amber glass prescription bottles were filled; three were stored in the refrigerator and three at room temperature. The mean temperatures ($\pm$ standard deviations) in these two environments over the course of the study were $3.0 \pm 1.3^\circ\text{C}$ and $25.2 \pm 1.6^\circ\text{C}$. All bottles were exposed only to the fluorescent lights in the laboratory.

Qualitative evaluation of physical appearance took place initially and at weekly intervals up to 91 days; aliquots were removed from all amber bottles and examined for colour changes and precipitates (against white and black backgrounds), odour changes, layering, sedimentation, caking, ease of resuspension, and gas formation. pH was also determined at the same time (footnote c). Immediately following these physical observations, each suspension bottle was manually shaken for 10 seconds, and initial and weekly samples were withdrawn.

These samples were stored in a -85°C freezer until batch-analysis by a stability-indicating high performance liquid chromatography (HPLC) method.(8) Our column, mobile phase, and chromatographic conditions were identical to the methods previously reported.(8) All samples were analyzed within a time period of less than one month.

For details on preparation of stock and standard solutions and preparation of samples, see **Appendix**.

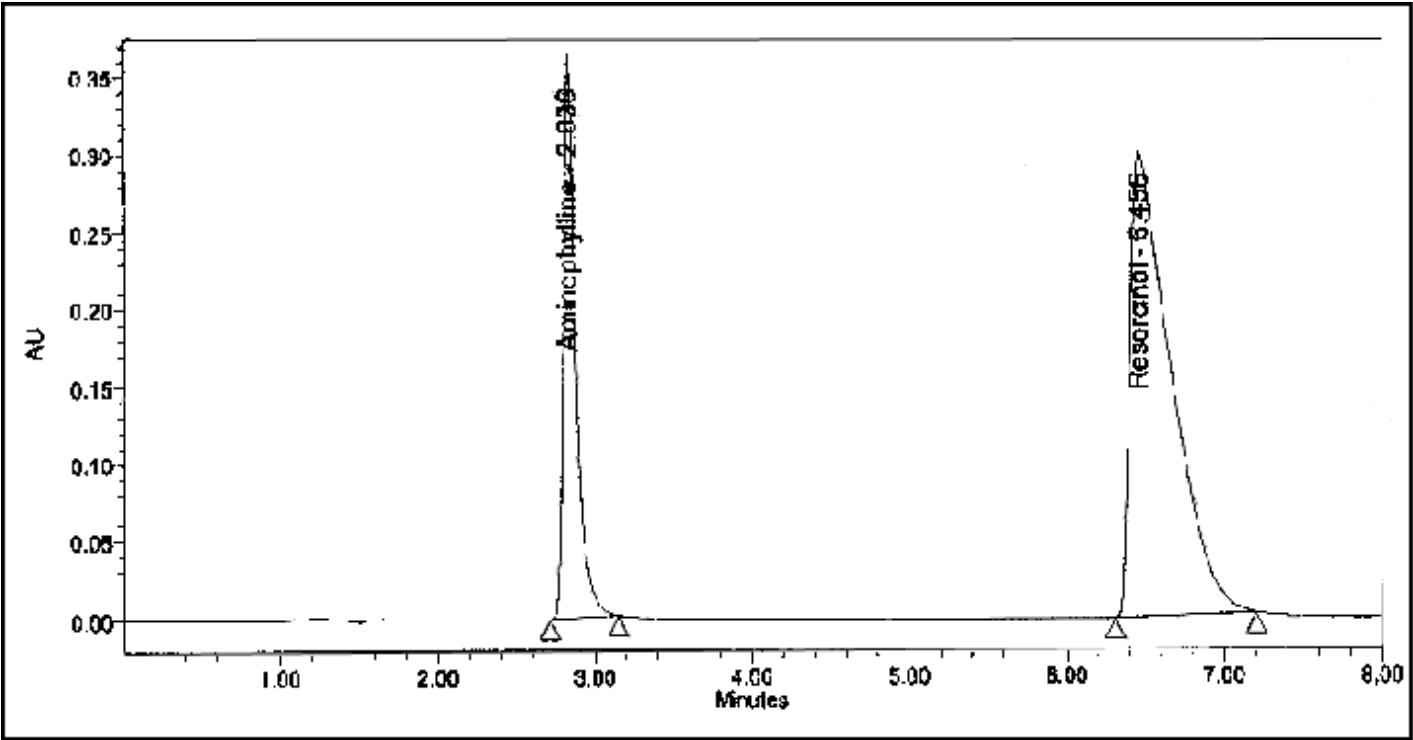
Results

The regression analysis of the HPLC assay validation showed linearity over the working range of concentrations [$r^2 > 0.999$ ($n=5$)]. The intra- and inter-day coefficients of variation (CV) for the three different concentrations were within the acceptable limits of $< 1\%$. For the 1 mg/mL standard solution, the CV for intra-day ($n=4$) and inter-day ($n=4$) variability were 0.08% and 0.65%, respectively; for the 3 mg/mL solution, the CV were 0.15% and 0.22%, respectively; and for the 5 mg/mL solution, the CV were 0.09% and 0.19%, respectively.

The qualitative evaluation of physical appearance showed no significant changes in the majority of suspensions. Throughout the study, most of the opaque white suspensions had a sweet smell and were easily resuspendable. The only exceptions were the 21 mg/mL suspensions at 4°C, which formed white needle-like crystals, variable in size, by Day 7. Over the course of 91 days, the pH of the 3 mg/mL samples ranged from 5.5 to 6.0; the pH range of the 21 mg/mL samples was 8.5 to 9.2. The mean pH $\pm$ standard deviations for these solutions were 5.7 ± 0.1 (3 mg/mL samples at 4°C), 5.6 ± 0.1 (3 mg/mL samples at 25°C), 9.0 ± 0.1 (21 mg/mL samples at 4°C), and 8.7 ± 0.1 (21 mg/mL samples at 25°C). Overall, no major changes in physical appearance, odour, or pH were observed, other than the aforementioned crystal formation.

The retention time of aminophylline was 2.8 minutes, while the internal standard, 5-methylresorcinol, was retained for 6.5 minutes (Figure 1).

FIGURE 1. Representative chromatogram, showing the aminophylline peak at 2.8 minutes and the 5-methylresorcinol peak at 6.5 minutes.



Results of the HPLC analysis show that the 3 mg/mL suspensions at both temperatures (4°C and 25°C) and the 21 mg/mL suspensions at 25°C maintained at least 90% of their initial concentrations; however, the 21 mg/mL suspensions at 4°C failed to maintain 90% of initial concentration (Table 1).

TABLE 1. Average percent remaining of the triplicate samples over 91 days.

Initial Concentration* (mg/mL)		2.80 $\pm$ 0.07	2.79 $\pm$ 0.07	19.21 $\pm$ 0.60	19.48 $\pm$ 0.11
Storage Temperature (°C)		4	25	4	25
% Remaining*	Day 7	99 $\pm$ 3.2	99 $\pm$ 4.5	81 $\pm$ 1.0	96 $\pm$ 2.9
	Day 14	102 $\pm$ 9.8	99 $\pm$ 1.5	80 $\pm$ 1.9	99 $\pm$ 0.8
	Day 21	95 $\pm$ 1.8	102 $\pm$ 6.5	76 $\pm$ 1.5	100 $\pm$ 0.5

Day 28	96 ± 7.4	91 ± 8.9	76 ± 5.3	94 ± 4.0
Day 35	94 ± 11.2	101 ± 6.1	77 ± 1.1	99 ± 1.5
Day 42	105 ± 2.6	103 ± 2.3	78 ± 0.5	101 ± 1.2
Day 49	102 ± 6.1	98 ± 0.5	76 ± 0.6	101 ± 0.4
Day 56	104 ± 13.8	103 ± 10.3	80 ± 6.4	99 ± 1.6
Day 63	100 ± 14.9	103 ± 2.5	77 ± 3.4	101 ± 1.5
Day 70	93 ± 4.1	97 ± 5.0	74 ± 1.3	101 ± 0.7
Day 77	93 ± 1.6	96 ± 1.3	75 ± 3.0	101 ± 0.9
Day 84	95 ± 5.3	95 ± 3.2	74 ± 1.7	100 ± 3.0
Day 91	100 ± 4.7	103 ± 6.1	82 ± 2.3	108 ± 1.2

*Mean ± standard deviation, n=3.

Discussion

To our knowledge, no published information regarding the stability of extemporaneously-prepared aminophylline in the Ora Sweet:Ora Plus vehicle existed prior to this study. We were able to demonstrate that the expiration date for aminophylline oral suspensions can be extended past the traditional 7-day empirically determined limit for methylcellulose suspensions. At the end of 91 days, we found aminophylline to be both chemically and physically stable in 1:1 Ora Sweet:Ora Plus as 3 mg/mL at 4°C and 25°C, and as 21 mg/mL at 25°C. The white needle crystal formation in the 21 mg/mL aminophylline suspensions at 4°C was unexpected. Most likely, this observation can be explained by temperature effects on drug solubility, ultimately leading to crystal growth. The crystal formation is also a probable explanation for the large drop in the percentage of drug remaining; since more drug has precipitated out as crystals, less is remaining in suspension (i.e. the portion from which the sample is taken). The instability of the refrigerated high concentration extemporaneous aminophylline suspensions may warrant the use of commercial theophylline preparations for adults who cannot tolerate oral solid dosage forms. This should not pose a problem since the additives used in commercial formulations pose less of a toxicity risk to adult patients.

The pH of the 3 mg/mL concentration was different from that of the 21 mg/mL suspensions. This is not surprising, given that the volume of the original 25 mg/mL injectable solution differs for the two concentrations. The 3 mg/mL required only a small volume of injectable aminophylline which resulted in a small change from the pH of the Ora Sweet:Ora Plus vehicle. However, the 21 mg/mL preparation was mostly injectable aminophylline and only a small amount of vehicle which resulted in a more alkaline pH.

Our preparation guidelines and storage recommendations for aminophylline suspensions in Ora Sweet:Ora Plus may enable improved patient care and reduced costs to the health-care system. Labour costs (i.e., pharmacy technician time) appear to be lower when the suspensions are prepared in Ora Sweet:Ora Plus as compared with preparation using methylcellulose. Since the vehicle is commercially available, community pharmacists can prepare the Ora Sweet:Ora Plus suspensions, negating the need for outpatients to return to our institution for this purpose. Although aminophylline tablets are likely more readily available in the community setting, the injection is advantageous since it overcomes the problem of incomplete tablet grinding or crushing, thus creating a more uniformly dispersed suspension. Lastly, the longer expiration dates (91 days versus 7 days) reduce the number of dispensing events, and consequently lower costs for the patient.

Conclusions

At the end of 91 days, aminophylline is both chemically and physically stable in 1:1 Ora Sweet:Ora Plus as 3 mg/mL at 4°C and 25°C, and as 21 mg/mL at 25°C. The expiration dates of these suspensions can be extended beyond our current practice of 7 days, leading to benefits for the patient, the pharmacy and the health-care system. Due to crystal formation, aminophylline suspensions prepared according to our methods in Ora Sweet:Ora Plus were not physically stable as 21 mg/mL at 4°C.

Acknowledgements

Many thanks to Mr. Al McDougal for his assistance in preparing the final manuscript. Much appreciation to Dr. Helen Burt for her scientific advising, and to Mr. John Jackson and Ms. Diane Decarie for their technical guidance.

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Appendix: Preparation of Stock and Standard Solutions, and Preparation of Samples

Preparation of stock and standard solutions

Aminophylline stock solutions of 1, 2, 3, 4, and 5 mg/mL were created by dissolving analytical-grade drug powder ([footnote d](#)) in 0.9% sodium chloride ([footnote e](#)). The 5 mg/mL stock solution was prepared by placing 1.25 g aminophylline powder in a volumetric flask, and bringing up to 250 mL with 0.9% sodium chloride.⁽⁸⁾ Aliquots of the 5 mg/mL stock solution were diluted to achieve the other four concentrations. Standard solutions were prepared by further diluting a 0.1 mL aliquot of each stock solution to 3 mL with mobile phase to obtain final concentrations of 0.033, 0.067, 0.100, 0.133, and 0.167 mg/mL. This dilution step was necessary in minimizing the absorbance of aminophylline at 254 nm to give optimal chromatographics. An internal standard, 5-methylresorcinol ([footnote f](#)) was used as an indicator for loss of sample and percent recovery. 5-methylresorcinol 1.5 mg/mL in HPLC-grade water was added 2:1 (v/v) to the standard solutions. Prior to injection, all standard solutions were passed through a 0.45 µm microfilter ([footnote g](#)).

The HPLC instrumentation ([footnote h](#)) consisted of a solvent delivery pump, an automatic injector equipped with a 200 mL injector, a Sentry 3.9 x 20 mm guard column, a Nova-Pak C18 3.9 x 150 mm column, and an ultraviolet detector ([footnote i](#)) set at 254 nm. The mobile phase was 10:1 (v/v) 0.1 M acetate buffer:acetonitrile, and the flow rate was 1 mL/min.⁽⁸⁾ The acetate buffer (pH range 3.4 to 3.9) was prepared by placing 50 mL of 0.1 M sodium acetate in a 1000 mL volumetric flask and diluting to volume with 0.1 M acetic acid.⁽⁸⁾ All solvents were HPLC-grade and filtered before use.

The HPLC validation involved a calibration curve with the 5 standard solutions (which had final concentrations of 0.033, 0.067, 0.100, 0.133, and 0.167 mg/mL) and a blank (0.9% sodium chloride) at the beginning of each run. The range of this calibration curve (0.033 to 0.167 mg/mL) encompasses the diluted concentrations of the 3 mg/mL and 21 mg/mL samples, all of which were diluted to nominal concentrations of 0.1 mg/mL; thus, the curve was used to analyze all samples. The calibration curve was generated by least-squares regression of the ratio of the peak area of aminophylline to that of 5-methylresorcinol versus the concentration of each standard solution. Precision and reproducibility of the assay were evaluated by running the 1, 3, and 5 mg/mL stock solutions (diluted to standards of 0.033, 0.100, and 0.167 mg/mL) in quadruplicate daily for 4 days. The means, standard deviations, and coefficients of variation (CV) were calculated. Acceptable limits were defined a priori as <1%.

Preparation of samples

During the assay phase of the study, the triplicate aminophylline oral suspension samples were processed in a similar manner as the stock solutions. A 0.1 mL aliquot of the 3 mg/mL samples was diluted to 3 mL with mobile phase to achieve a final concentration of 0.1 mg/mL, while a 0.02 mL aliquot of the 21 mg/mL samples was diluted to 4.2 mL, again resulting in a final concentration of 0.1 mg/mL. 5-methylresorcinol 1.5 mg/mL in HPLC-grade water was added 2:1 (v/v) to the diluted 3 mg/mL samples; 5-methylresorcinol 7.5 mg/mL in HPLC-grade water was added to the diluted 21 mg/mL samples. All samples were passed through a 0.45 µm microfilter ([footnote g](#)) before injecting a 45 µL sample onto the column. Percent of initial drug concentration remaining was calculated for each sample. Stability was defined as maintenance of at least 90% of the initial drug concentration.

Footnotes

^a Ora Sweet:Ora Plus, Paddock Laboratories Inc., Minneapolis, MN

^b Aminophylline injection 25 mg/mL, Abbott Laboratories Ltd., Montreal, QC

^c pH meter, VWR Scientific Model 8000, West Chester, PA

^d Analytical-grade aminophylline powder, Sigma-Aldrich Canada Ltd., Oakville, ON

^e Sodium chloride 0.9%, Baxter, Toronto, ON

^f 5-Methylresorcinol, Orcinol, Sigma-Aldrich Canada Ltd., Oakville, ON

^g Acrodisc GHP syringe filter, Gelman, Ann Arbor, MI

^h Waters Alliance System, Waters Ltd., Mississauga, ON

ⁱ 2487 Dual Wavelength Absorbance Detector, Waters Ltd., Mississauga, ON

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Original Research Article

Stability of Aminophylline in Extemporaneously-Prepared Oral Suspensions

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Abstract

Rationale: Oral aminophylline liquid formulations are not available in Canada. The advent of a commercially-available vehicle (1:1 Ora Sweet:Ora Plus) provides an alternative to extemporaneous compounding, but stability information is unavailable for aminophylline in oral suspensions prepared with this newer vehicle.

Objectives: To evaluate the stability of aminophylline 3 mg/mL (pediatric) and 21 mg/mL (adult) in the Ora Sweet:Ora Plus vehicle, at 4°C and 25°C, over a period of 91 days.

Methods: Triplicate suspensions were prepared in 50 mL amber glass prescription bottles using aminophylline injection 25 mg/mL. For each concentration, six bottles were filled; three were stored at 4°C (refrigerated) and three at 25°C (room temperature). Samples were removed from each bottle initially and at weekly intervals, at which time their physical appearance, odour, and pH were also examined. The samples were stored in a -85°C freezer until batch-analysis by a validated stability-indicating high performance liquid chromatography (HPLC) assay using ultraviolet detection at 254 nm. Percent of initial drug concentration remaining was calculated for each sample. Stability was defined as

maintenance of at least 90% of initial drug concentration.

Results: The majority of the opaque white suspensions had a sweet smell and were easily resuspendable; however, the 21 mg/mL suspensions stored at 4°C formed white needle crystals within 7 days. Other than the crystal formation, no significant changes in physical appearance, odour, or pH were observed over the course of the study. The results of the HPLC analysis revealed that the 3 mg/mL suspensions at both temperatures (4°C and 25°C) and the 21 mg/mL suspensions at 25°C maintained at least 90% of their initial concentrations. However, the 21 mg/mL suspensions stored at 4°C failed to maintain 90% of initial concentration.

Conclusions: At the end of 91 days, aminophylline is both chemically and physically stable in 1:1 Ora Sweet:Ora Plus as a 3 mg/mL suspension stored at 4°C and 25°C, and as a 21 mg/mL suspension stored at 25°C. Accordingly, the expiration dates of these specific suspensions can be extended to 90 days.

J Inform Pharmacother 2000;2:100-6.

Aminophylline, the ethylenediamine salt equivalent to 79% theophylline, has long been used in pulmonary diseases including asthma, chronic

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bronchitis, and emphysema. In our hospital, aminophylline is primarily used as a respiratory stimulant for first-line treatment of apnea of prematurity.(1) Solid oral dosage forms of aminophylline are undesirable in this pediatric population.

While several liquid formulations of aminophylline are marketed in the United States, none are commercially available in Canada.(2,3) Liquid theophylline preparations are available in Canada (e.g. Theolair® liquid (3M), Theophylline elixir (Technilab) and Theophylline solution (Desbergers)(3); however, in some institutions such as ours, these preparations are not used due to concerns about potential excipient-related toxicities.

Commercially-available theophylline solution products contain excipients (e.g., sorbitol, alcohol, propylene glycol) that are inappropriate for the pediatric population, particularly the neonatal and infant age groups. Specifically, Theolair® contains sorbitol which may be associated with gastrointestinal side effects such as osmotic diarrhea and abdominal pain.(4,5) The alcohol content in theophylline elixir combined with the reduced activity of alcohol dehydrogenase in children may result in accumulation and potential acute toxicity until this enzyme system reaches adult levels of activity.(4) Theophylline solutions that contain propylene glycol may put premature infants at risk for displacement of bilirubin and consequently hyperbilirubinemia.(4,5,6) Excessive intake of propylene glycol and subsequent metabolism to lactic acid may also cause the development of hyperosmolality and lactic acidosis.(4,6) Other additives such as flavouring agents and dyes may also be problematic.(4,5,6)

As a result of our reluctance to use commercially available products, we extemporaneously compound oral aminophylline preparations for use in our pediatric patients. To date, our oral aminophylline suspensions have been prepared in a methylcellulose vehicle and given, based on historical procedures, an empirical expiration date of 7 days. The methylcellulose suspensions present some significant problems, including intensive labour, inability by community pharmacists to prepare, short expiration dates and inconvenience to outpatients; all of these

factors are expected to lead to increased costs to the health-care system.

A commercially-available vehicle (1:1 mixture of Ora Sweet:Ora Plus (footnote a), a syrup and suspending agent, respectively) has recently emerged as an alternative to methylcellulose. Ora Sweet (footnote a) contains purified water, sucrose, glycerin, sorbitol, and flavoring, with citric acid and sodium phosphate as buffers, and methylparaben and potassium sorbate as preservatives. Ora Plus (footnote a) contains purified water, microcrystalline cellulose, carboxymethylcellulose sodium, xanthan gum, carrageenan, citric acid and sodium phosphate as buffers, simethicone as an antifoaming agent, and methylparaben and potassium sorbate as preservatives. Ora Sweet:Ora Plus has been widely accepted as a suitable vehicle for use in the pediatric population due to the lack of inappropriate additives. Furthermore, this newer vehicle is expected to eliminate many of the disadvantages associated with methylcellulose, since it is reportedly easier to work with and more readily available in the community. However, stability information for aminophylline in Ora Sweet:Ora Plus is not currently available.

Pharmaceutical stability is defined as the extent to which a product retains, within specified limits and throughout its period of storage and use (i.e., shelf-life), the same properties and characteristics that it possessed at the time of manufacture.(7) The types of stability pertinent to our study include chemical and physical stability. Chemical stability refers to the integrity and labeled potency of the active ingredient and physical stability refers to the maintenance of the original physical properties and appearance.

Objective

The objective of the study was to evaluate the stability of aminophylline 3 mg/mL (pediatric) and 21 mg/mL (adult) in oral suspensions, extemporaneously prepared with the Ora Sweet:Ora Plus vehicle at 4°C and 25°C over a period of 91 days.

Methods

Preparation of oral suspensions

The suspensions were prepared in triplicate using commercially-available aminophylline injection 25 mg/mL (footnote b) in the 1:1 Ora Sweet:Ora Plus vehicle. The 3 mg/mL (pediatric) and 21 mg/mL (adult) concentrations represent those used in clinical practice. For each concentration, six 50 mL amber glass prescription bottles were filled; three were stored in the refrigerator and three at room temperature. The mean temperatures ($\pm$ standard deviations) in these two environments over the course of the study were $3.0 \pm 1.3^\circ\text{C}$ and $25.2 \pm 1.6^\circ\text{C}$. All bottles were exposed only to the fluorescent lights in the laboratory.

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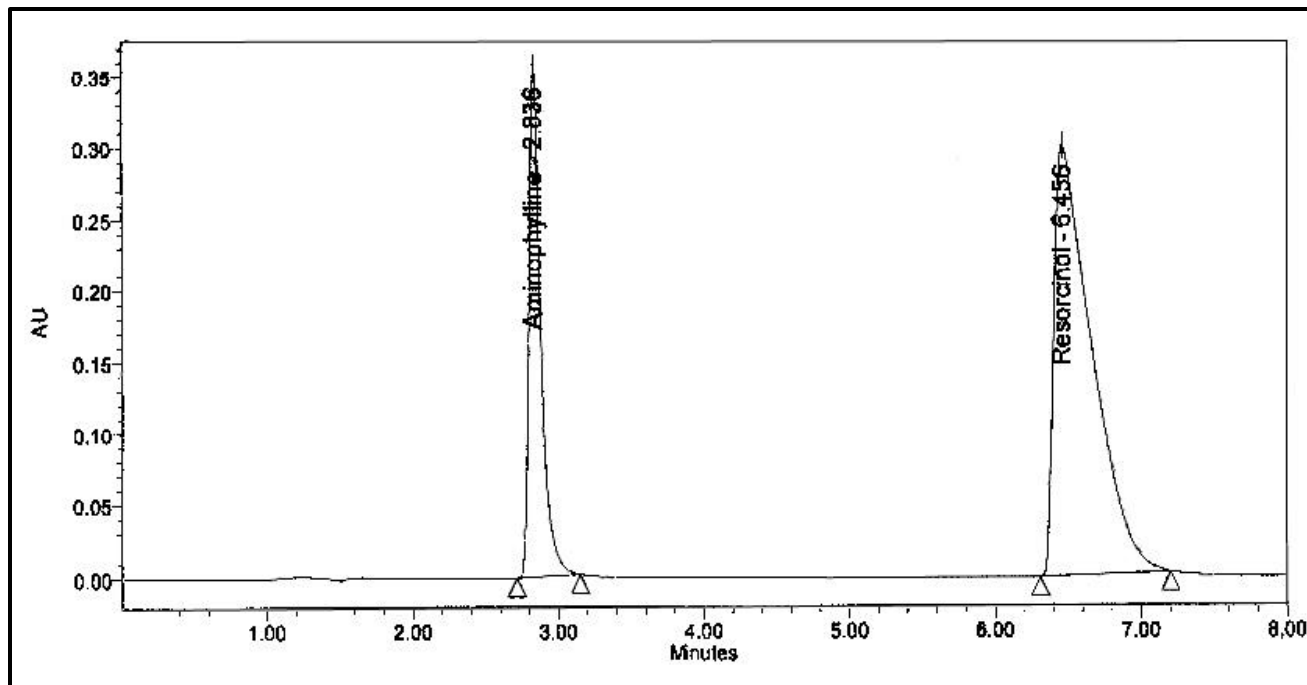
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For details on preparation of stock and standard solutions and preparation of samples, see Appendix.

Results

The regression analysis of the HPLC assay validation

Figure 1. Representative chromatogram, showing the aminophylline peak at 2.8 minutes and the 5-methylresorcinol peak at 6.5 minutes.



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Table 1. Average percent remaining of the triplicate samples over 91 days.

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*Mean ± standard deviation, n=3.

showed linearity over the working range of concentrations [$r^2 > 0.999$ (n=5)]. The intra- and inter-day coefficients of variation (CV) for the three different concentrations were within the acceptable limits of < 1%. For the 1 mg/mL standard solution, the CV for intra-day (n=4) and inter-day (n=4) variability were 0.08% and 0.65%, respectively; for the 3 mg/mL solution, the CV were 0.15% and 0.22%, respectively; and for the 5 mg/mL solution, the CV were 0.09% and 0.19%, respectively.

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Discussion

To our knowledge, no published information regarding the stability of extemporaneously-prepared aminophylline in the Ora Sweet:Ora Plus vehicle existed prior to this study. We were able to demonstrate that the expiration date for aminophylline oral suspensions can be extended past the traditional 7-day empirically determined limit for methylcellulose suspensions. At the end of 91 days, we found aminophylline to be both chemically and physically stable in 1:1 Ora Sweet:Ora Plus as 3 mg/mL at 4°C and 25°C, and as 21 mg/mL at 25°C.

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The white needle crystal formation in the 21 mg/mL aminophylline suspensions at 4°C was unexpected. Most likely, this observation can be explained by temperature effects on drug solubility, ultimately leading to crystal growth. The crystal formation is also a probable explanation for the large drop in the percentage of drug remaining; since more drug has precipitated out as crystals, less is remaining in suspension (i.e., the portion from which the sample is taken). The instability of the refrigerated high concentration extemporaneous aminophylline suspensions may warrant the use of commercial theophylline preparations for adults who cannot tolerate oral solid dosage forms. This should not pose a problem since the additives used in commercial formulations pose less of a toxicity risk to adult patients.

The pH of the 3 mg/mL concentration was different from that of the 21 mg/mL suspensions. This is not surprising, given that the volume of the original 25 mg/mL injectable solution differs for the two concentrations. The 3 mg/mL required only a small volume of injectable aminophylline which resulted in a small change from the pH of the Ora Sweet:Ora Plus vehicle. However, the 21 mg/mL preparation was mostly injectable aminophylline and only a small amount of vehicle which resulted in a more alkaline pH.

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Conclusions

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Appendix

Preparation of Stock and Standard Solutions, and Preparation of Samples

Preparation of stock and standard solutions

Aminophylline stock solutions of 1, 2, 3, 4, and 5 mg/mL were created by dissolving analytical-grade drug powder (footnote d) in 0.9% sodium chloride (footnote e). The 5 mg/mL stock solution was prepared by placing 1.25 g aminophylline powder in a volumetric flask, and bringing up to 250 mL with 0.9% sodium chloride.(8) Aliquots of the 5 mg/mL stock solution were diluted to achieve the other four concentrations. Standard solutions were prepared by further diluting a 0.1 mL aliquot of each stock solution to 3 mL with mobile phase to obtain final concentrations of 0.033, 0.067, 0.100, 0.133, and 0.167 mg/mL. This dilution step was necessary in minimizing the absorbance of aminophylline at 254 nm to give optimal chromatographics. An internal standard, 5-methylresorcinol (footnote f) was used as an indicator for loss of sample and percent recovery. 5-methylresorcinol 1.5 mg/mL in HPLC-grade water was added 2:1 (v/v) to the standard solutions. Prior to injection, all standard solutions were passed through a 0.45 µm microfilter (footnote g).

The HPLC instrumentation (footnote h) consisted of a solvent delivery pump, an automatic injector equipped with a 200 mL injector, a Sentry 3.9 x 20 mm guard column, a Nova-Pak C18 3.9 x 150 mm column, and an ultraviolet detector (footnote i) set at 254 nm. The mobile phase was 10:1 (v/v) 0.1 M acetate buffer:acetonitrile, and the flow rate was 1 mL/min.(8) The acetate buffer (pH range 3.4 to 3.9) was prepared by placing 50 mL of 0.1 M sodium acetate in a 1000 mL volumetric flask and diluting to volume with 0.1 M acetic acid.(8) All solvents were HPLC-grade and filtered before use.

The HPLC validation involved a calibration curve with the 5 standard solutions (which had final concentrations of 0.033, 0.067, 0.100, 0.133, and 0.167 mg/mL) and a blank (0.9% sodium chloride) at the beginning of each run. The range of this calibration curve (0.033 to 0.167 mg/mL) encompasses the diluted concentrations of the 3 mg/mL and 21 mg/mL samples, all of which were diluted to nominal concentrations of 0.1 mg/mL; thus, the curve was used to analyze all samples. The calibration curve was generated by least-squares regression of the ratio of the peak area of aminophylline to that of 5-methylresorcinol versus the concentration of each standard solution. Precision and reproducibility of the assay were evaluated by running the 1, 3, and 5 mg/mL stock solutions (diluted to standards of 0.033, 0.100, and 0.167 mg/mL) in quadruplicate daily for 4 days. The means, standard deviations, and coefficients of variation (CV) were calculated. Acceptable limits were defined a priori as < 1%.

Preparation of samples

During the assay phase of the study, the triplicate aminophylline oral suspension samples were processed in a similar manner as the stock solutions. A 0.1 mL aliquot of the 3 mg/mL samples was diluted to 3 mL with mobile phase to achieve a final concentration of 0.1 mg/mL, while a 0.02 mL aliquot of the 21 mg/mL samples was diluted to 4.2 mL, again resulting in a final concentration of 0.1 mg/mL. 5-methylresorcinol 1.5 mg/mL in HPLC-grade water was added 2:1 (v/v) to the diluted 3 mg/mL samples; 5-methylresorcinol 7.5 mg/mL in HPLC-grade water was added to the diluted 21 mg/mL samples. All samples were passed through a 0.45 µm microfilter (footnote g) before

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injecting a 45 μ L sample onto the column. Percent of initial drug concentration remaining was calculated for each sample. Stability was defined as maintenance of at least 90% of the initial drug concentration.

Footnotes

- a. Ora Sweet:Ora Plus, Paddock Laboratories Inc., Minneapolis, MN
- b. Aminophylline injection 25 mg/mL, Abbott Laboratories Ltd., Montreal, QC
- c. pH meter, VWR Scientific Model 8000, West Chester, PA
- d. Analytical-grade aminophylline powder, Sigma-Aldrich Canada Ltd., Oakville, ON
- e. Sodium chloride 0.9%, Baxter, Toronto, ON
- f. 5-Methylresorcinol, Orcinol, Sigma-Aldrich Canada Ltd., Oakville, ON
- g. Acrodisc GHP syringe filter, Gelman, Ann Arbor, MI
- h. Waters Alliance System, Waters Ltd., Mississauga, ON
- i. 2487 Dual Wavelength Absorbance Detector, Waters Ltd., Mississauga, ON

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2000;2:200-202.

Doxazosin versus chlorthalidone: What can we learn from the early results of the ALLHAT trial?

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Reviewer: Nancy Cherry, B.Sc.(Pharm)

Reviewer's email address: nancy_cherry@hotmail.com

Reviewer's profession/specialty: Hospital Pharmacy Resident

Original Citation

ALLHAT Collaborative Research Group. Major Cardiovascular Events in Hypertensive Patients Randomized to Doxazosin versus Chlorthalidone - The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) JAMA 2000;283:1967-75. [PubMed Cit](#)

Overall Study Question

The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is a double-blind, randomized, practice-based clinical trial involving over 40,000 high-risk hypertensive patients aged 55 years and older. Sponsored by the National Heart, Lung and Blood Institute and the U.S. Department of Veterans' Affairs, this trial has two components; the antihypertensive agent assessment and the lipid-lowering agent assessment. The objective of the antihypertensive component of ALLHAT was to determine whether the combined incidence of fatal coronary heart disease (CHD) and nonfatal myocardial infarction differs between persons randomized to diuretic (chlorthalidone) treatment and each of three alternative treatments - a calcium antagonist (amlodipine), an angiotensin converting enzyme inhibitor (lisinopril), and an alpha-adrenergic blocker (doxazosin). The results of the prematurely-terminated doxazosin arm of the trial are presented here.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. The results presented in this study are only representative of the doxazosin arm of ALLHAT. The study investigators randomized participants using a computer-generated

schedule to one of four treatments: chlorthalidone, amlodipine, lisinopril, or doxazosin, in a ratio of 1.7:1:1:1, respectively. Randomization was stratified by center and blocked over time to maintain the ratio. The ALLHAT Clinical Trials Center held the randomization code.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. 42,448 patients met the inclusion criteria and were randomized to one of the four treatment groups. Of the 15,268 patients who received chlorthalidone, 501 were lost to follow-up, 851 died (633 non-CHD deaths and 218 CHD deaths) and the remaining patients are still being followed as part of the ongoing ALLHAT. Of the 9,067 patients who received doxazosin, 338 were lost to follow-up and 514 died (384 non-CHD deaths and 130 CHD deaths). Patients who were also enrolled in the lipid-lowering trial component of ALLHAT continue to be followed.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. Initially, all parties were blinded; however, once a patient reached the maximum dose and did not meet the BP goal, an open-label Step 2 agent (atenolol, reserpine or clonidine) or an open-label Step 3 agent (hydralazine) was added.

4. Were the groups similar at the start of the trial?

Yes. The large sample size and randomization process resulted in similar baseline characteristics across the chlorthalidone and doxazosin treatment groups.

5. Aside from the experimental intervention, were the groups treated equally?

Yes. All patients were followed every three months during the first year of enrollment and every four months thereafter.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

The primary outcome for the hypertension component of ALLHAT was the composite of fatal CHD and nonfatal MI. No significant difference was found between the

chlorthalidone and doxazosin treatment groups with regards to the primary outcome. Fatal CHD or non-fatal MI: RR=1.03, P=0.71. Secondary outcomes included all-cause mortality, combined CHD, stroke and combined cardiovascular disease (CVD). No significant difference was observed for all-cause mortality (RR=1.03, P=0.56). However, significant differences were observed with the three other secondary endpoints: combined CHD (RR=1.1, P=0.05, 95% CI= 1.00-1.12), stroke (RR=1.19, P<0.001, 95% CI= 1.01-1.40) and combined CVD (RR=1.25, P=0.04, 95% CI= 1.17-1.33). Results for combined CVD were further broken down to reveal significant differences between the two treatment groups for congestive heart failure (CHF) (RR=2.04, P<0.001, 95% CI= 1.79-2.32), coronary revascularization (RR=1.15, P=0.05, 95% CI=1.00-1.32), and angina (RR=1.16, P<0.001, 95% CI= 1.05-1.27). No significant difference was observed in peripheral artery disease (RR=1.07, P=0.50, 95% CI=0.88-1.30).

2. How precise was the estimate of the treatment effect?

The only significant difference observed was with the secondary outcome of combined CVD. The 95% CI were narrow (RR=1.25, 95% CI= 1.17-1.33).

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. The inclusion criteria were very broad and the results of this trial can be applied to a wide range of patients who have hypertension. The inclusion criteria included both men and women aged 55 years and older who had systolic blood pressure (SBP) of at least 140mmHg and/or diastolic blood pressure (DBP) of at least 90mmHg, or took medication for hypertension and had at least one additional risk factor for CHD. These risk factors included previous MI or stroke, left ventricular hypertrophy by electrocardiogram or echocardiogram, history of type 2 diabetes, current cigarette smoking, and low high-density lipoprotein cholesterol level. Exclusion criteria included symptomatic MI or stroke within the past six months, symptomatic CHF or ejection fraction<35%, angina pectoris within the past six months, requirements for any of the study treatment drugs for any reason other than hypertension, current requirement for more than two antihypertensive medications, and SBP>180mmHg or DBP>110mmHg on two separate readings.

2. Were all clinically important outcomes considered?

Yes. All major cardiac endpoints were considered including fatal CHD and non-fatal MI, all-cause mortality, combined CHD, stroke, CHF, coronary revascularization, angina and peripheral vascular disease.

3. Are the likely treatment benefits worth the potential harms and costs?

Yes. It appears that doxazosin is associated with a greater risk of combined cardiovascular events, particularly CHF in high-risk hypertensive patients compared to chlorthalidone. However, it is important to note that these differences were observed in a secondary outcome while no

difference was observed in the primary outcome, namely fatal CHD or non-fatal MI. No difference was observed in any other secondary outcome or all-cause mortality.

Commentary

This study shows that when compared with doxazosin, chlorthalidone therapy appears to yield an essentially equal risk of CHD death/nonfatal MI (primary outcome), but significantly reduces the risk of combined CVD events. This was particularly evident for CHF in high-risk hypertensive patients. However, it is important to recognize that no difference was observed in the primary outcome, only in one of four secondary outcomes. Another limitation of this study is that it does not address the issue of class effect and whether or not all alpha-blockers should be avoided in the treatment of hypertension. The US-JNC, CMA, WHO and the British Hypertension Society all consider alpha-blockers as equally efficacious as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and calcium channel blockers when used for antihypertensive effects. If the results of this study are adopted, these guidelines will need to be amended.

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Doxazosin versus chlorthalidone: What can we learn from the early results of the ALLHAT trial?

Reviewer: Nancy Cherry, B.Sc.(Pharm)

Reviewer's email address: nancy_cherry@hotmail.com

Reviewer's profession/specialty: Hospital Pharmacy Resident, Vancouver Hospital and Health Sciences Centre, Vancouver, B.C., Canada

Original Citation

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J Inform Pharmacother 2000;2:200-202.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2000;2:203-205.

Elderly depression: Is a SSRI no better than a TCA for this late-life disorder?

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Reviewer: David Gardner, Pharm.D.

Reviewer's email address: david.gardner@dal.ca

Reviewer's profession/specialty: Psychopharmacology

Original Citation

Mulsant BH, Pollock BG, Nebes RD, Miller MD, Little JT, Stack J, Houck PR, Bensasi S, Mazumdar S, Reynolds CF 3rd. A double-blind randomized comparison of nortriptyline and paroxetine in the treatment of late-life depression: 6-week outcome. *J Clin Psychiatry* 1999;60 Suppl 20:16-20. [PubMed Citation](#)

Overall Study Question

In mild to moderately depressed elderly inpatients and outpatients, is there a difference in clinical effectiveness between selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants (TCA)?

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Randomized and stratified based on inpatient vs. outpatient status and baseline mini mental status score (24 or below vs. 25 or above).

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. Eighty consenting patients (43 nortriptyline (NOR) and 37 paroxetine (PAR)) received at least one dose of a randomly allocated treatment regimen and this represented the

intention to treat study group. Two analyses were completed, one for the intention to treat group and the second for a "completer" group.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Unable to determine. The authors stated that patient were "assigned to treatment under double-blind conditions", however, they did not clarify whether dosage forms were identical. Nortriptyline was given at night and was adjusted according to response and serum drug concentrations. Conversely, paroxetine was given in the morning. Dosing strategies differed based on inpatient vs. outpatient status. Considering these differences in dosing methods, it is difficult to understand how blinding was established and maintained. The authors did not discuss any tests to determine the effectiveness of the blinding procedures.

4. Were the groups similar at the start of the trial?

Overall, yes. However there were some notable differences between groups including differences in onset of illness (NOR 62.4 years vs. PAR 54.0, $p=0.06$) and incidence of patients with recurrences (49 NOR 49% vs. PAR 58%). Baseline depression scores (17 item HAM-D), cognitive functioning (MMSE) and duration of episodes were similar between groups.

5. Aside from the experimental intervention, were the groups treated equally?

Generally, yes. However, the nortriptyline dosing was adjusted based on feedback from serum levels and the authors did not state whether or not the paroxetine patients had mock serum levels undertaken in order to maintain similar procedures between groups.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

Eighty patients completed this 6-week study. The mean age was 75 years and the average HAM-D 17 score at baseline was 22.5. There were no significant differences between the two treatments in terms of antidepressant response (as measured by change in HAM-D score) or the proportion of patients achieving a HAM-D score of 10 (by intention to treat or per protocol analyses). The side effect burden (as measured by the UKU side effects scale) was similar among completers who received at least 4 weeks of treatment. 14/43 PAR recipients and 10/37 NOR recipients dropped out of the study prematurely, with 8/43 and 5/37 discontinuing therapy due to adverse drug reactions, respectively.

These differences were not significant.

2. How precise was the estimate of the treatment effect?

Not applicable.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. Depression is common among the elderly. In this study, patients were excluded if they had an obvious contraindication to either of the interventions or had a recent history of alcohol dependence or misuse. Included were patients with a presumptive diagnosis of dementia, as long as their MMSE was greater than 17. The investigators dosed both drugs appropriately, including adjusting nortriptyline doses based on target levels of 50-150 ng/mL. Lorazepam was given for anxiety or insomnia.

2. Were all clinically important outcomes considered?

The authors appropriately focused on the relevant outcomes of response and tolerability. The authors also categorically evaluated the proportion of patients who achieved "near remission" (HAM D < 10). Considering the population sampled, an evaluation of cognitive functioning (MMSE) was prudent. However, the study did not address some important outcomes including: recurrence rates (i.e. stability of response), functional status, quality of life or pharmacoeconomic impact. To do so, a larger study of involving longer term assessments would be required. The authors will be reporting the 12-week results at a later date, however, this will not fully address these methodological shortcomings.

3. Are the likely treatment benefits worth the potential harms and costs?

Unable to determine. For most patients, SSRI are now used as first line treatment more commonly than most other antidepressants (especially the TCA) and this includes the treatment of elderly patients. The equivocal findings of this study in terms of both effect and tolerance suggest, as do many other studies, that the abandonment of the TCA in the last decade has been premature. Based on the average daily doses used in this study (NOR 51 mg and PAR 23 mg), the difference in drug acquisition cost is approximately three-fold. This difference is likely to be important to individuals who must pay for their medications and to third-party payers. It is not possible to determine from this study the pharmacoeconomic impact (from a societal perspective) of selectively using either one of these agents in the treatment of depression in the elderly. To do so, a much larger study involving a longer assessment period with a more precise evaluation of small differences in benefits, harms and costs.

Commentary

This study was rigorously designed and advances the clinicians knowledge of how SSRI and TCA compare in the elderly. Some studies concluded that TCA were superior to SSRI in the severely depressed elderly. A regression analysis completed by the authors of this study did not reveal that response was associated with treatment choice or severity of depression. The previous studies had major design flaws. The primary limitation of this current study is its short duration of outcome evaluation. This is important as treatment response can be delayed in the elderly. The authors have now presented the 12-week follow-up outcome data (American Psychiatric Association meeting, Chicago, USA, May 2000) and found that the earlier lack of difference in overall treatment response between groups persisted. These findings indicate that TCA and SSRI appear to be equally effective in the elderly with mild to moderate depression, and that choice should be based on factors other than "probability of responding to and tolerating treatment".

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Elderly depression: Is a SSRI no better than a TCA for this late-life disorder?

Reviewer: David Gardner, Pharm.D.

Reviewer's email address: david.gardner@dal.ca

Reviewer's profession/specialty: Psychopharmacology, Assistant Professor, Dalhousie Department of Psychiatry, Clinical Pharmacy Specialist (Psychiatry), Queen Elizabeth II Health Sciences Centre (QE II HSC), Halifax, Nova Scotia, Canada.

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Unable to determine. For most patients, SSRI are now used as first line treatment more commonly than most other antidepressants (especially the TCA) and this includes the treatment of elderly patients. The equivocal findings of this study in terms of both effect and tolerance suggest, as do many other studies, that the abandonment of the TCA in the last decade has been premature. Based on the average daily doses used in this study (NOR 51 mg and PAR 23 mg), the difference in drug acquisition cost is approximately three-fold. This difference is likely to be important to individuals who must pay for their medications and to third-party payers. It is not possible to determine from this study the pharmacoeconomic impact (from a societal perspective) of selectively using either one of these agents in the treatment of depression in the elderly. To do so, a much larger study involving a longer assessment period with a more precise evaluation of small differences in benefits, harms and costs.

J Inform Pharmacother 2000;2:203-205

Commentary

This study was rigorously designed and advances the clinician's knowledge of how SSRI and TCA compare in the elderly. Some studies concluded that TCA were superior to SSRI in the severely depressed elderly. A regression analysis completed by the authors of this study did not reveal that response was associated with treatment choice or severity of depression. The previous studies had major design flaws. The primary limitation of this current study is its short duration of outcome evaluation. This is important as treatment response can be delayed in the elderly. The authors have now presented the 12-week follow-up outcome data (American Psychiatric Association meeting, Chicago, USA, May 2000) and found that the earlier lack of difference in overall treatment response between groups persisted. These findings indicate that TCA and SSRI appear to be equally effective in the elderly with mild to moderate depression, and that choice should be based on factors other than "probability of responding to and tolerating treatment".

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2000;2:206-208.

Cost-effectiveness of treating type 2 diabetes with angiotensin-converting enzyme inhibitors: Should all patients receive this agent?

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Reviewer: Lila Assiff, M.Sc., and Jeffrey A. Johnson, Ph.D.

Reviewer's email address: jajohnson@pharmacy.ualberta.ca

Reviewer's profession/specialty: Researchers, Health Outcomes Research

Original Citation

Golan L, Birkmeyer JD, and Gilbert H. The cost-effectiveness of treating all patients with type 2 diabetes with angiotensin-converting enzyme inhibitors. Ann Intern Med 1999;131:660-7 [PubMed Citation](#)

Overall Study Question

The objective of this study was to determine the cost-effectiveness of treating all newly diagnosed type 2 diabetic patients with ACE inhibitors. A Markov model was used to simulate the progression of diabetic nephropathy in a hypothetical cohort of type 2 diabetics. Patients were assumed to be 50 years old at the time of their diagnoses and were followed through their lifetime. Lifetime cost, quality adjusted life years (QALY) and marginal cost effectiveness ratios were calculated for the 3 interventions including: 1) a "treat-all" category where patients were not screened and start receiving ACE inhibitor therapy at the time of diagnosis of diabetes; 2) screen for microalbuminuria-patients intervention where patients were screened for microalbuminuria and treatment is attempted in all patients whose tests result is positive; and, 3) a screen for gross proteinuria > intervention where patients are screened and treated if results are positive.

Are the Results of the Study Valid?

1. Did the analysis provide a full economic comparison of health care strategies?

Yes. This study provided a full economic evaluation and considered the cost and outcomes for each intervention, from the societal perspective, and included both a cost

effectiveness and a cost utility analysis. The analysis included Quality Adjusted Life Years (QALYs) and a cost utility measure (cost/QALYs gained). Incremental analyses were performed, and the three interventions were compared to each other.

2. Were the costs and outcomes properly measured and valued?

Yes. The costs considered were the health care costs associated with ACE inhibitor therapy, screening, and treatment of end stage renal disease (ESRD). The authors assumed that other health-related costs of diabetes were otherwise the same for the three intervention strategies. The costs seem to have been taken from appropriate U.S. sources (e.g., Medicare Clinical Diagnostic Fee Schedule), but the economic evaluation was taken from a Canadian perspective and therefore the costs may not be appropriate. Since so few clinical studies have been conducted on this topic, and since good clinical data would require a large cohort followed over a long period of time, the Markov model used in this study was appropriate. The main outcome measures were average lifetime cost; life expectancy; and quality adjusted life expectancy. From this, the marginal (i.e. incremental) cost-effectiveness was calculated for each strategy. Health related QOL was taken from literature and included diabetes-specific QOL scores, therefore seems appropriate. A discount rate of 3% was used for all costs and health benefits. The cost-effectiveness data was limited to type 2 diabetes, and the data from the Markov model used was based on the results of only 1 clinical trial that was conducted on Type 1 diabetics. The authors were as specific as possible without doing a primary clinical study, and recognized the potential limitations of the model.

3. Was appropriate allowance made for uncertainties in the analysis?

Yes. Extensive sensitivity analyses were performed. The authors indicate that the results were sensitive to cost of drugs, effectiveness of interventions, and estimates of HRQOL impact, but not sensitive to the costs of treating ESRD. The ranges tested in the sensitivity analyses were fairly wide and therefore the sensitivity analyses were appropriate.

4. Are estimates of costs and outcomes related to the baseline risk in the treatment population?

Yes. A sub-group analysis was not explicitly done, but within the sensitivity analyses, the age at diagnosis and the relative risk of progression to microalbuminuria were varied to determine the impact of those > risk factors on cost and QALYs gained. The benefit of treating all patients decreased and the marginal cost-effectiveness ratio increased when ACE inhibitors became less efficacious. Therefore, the earlier the age of diagnosis, the more "economically attractive" the "treat all" strategy was shown to be.

What are the Results?

1. What were the incremental costs and outcomes of each strategy?

STRATEGY: Screen for gross proteinuria: average cost: \$19520 life years: 15.38 QALY: 11.59 Cost Effectiveness: dominated. STRATEGY: Screen for microalbuminuria average cost: \$14940 life years: 15.59 QALY: 11.78 Cost Effectiveness: base case. STRATEGY: Treat all average cost: \$15240 life years: 15.63 QALY: 11.82 Cost Effectiveness: \$7500/QALYs gained. Since the "screen for microalbuminuria" intervention had the lowest cost, it was used as the reference case, and compared to this intervention, the treat-all strategy was more expensive but was associated with the highest life expectancy (i.e. it was dominated).

2. Do incremental costs and outcomes differ between sub-groups?

Yes. Again, under the sensitivity analyses, the cost-effectiveness of the "treat all" strategy compared to the screening for microalbuminuria strategy was sensitive to age at diagnosis of diabetes, cost of ACE inhibitors, relative risk for progression to microalbuminuria and HRQOL adjustment. The incremental costs and outcomes increased with increasing age. The ratio for the treat all strategy exceeded \$20,000/QALY if the patients age at diagnosis was 55 years or older. However, if the age of diagnosis is 44 years or younger, the treat all intervention becomes the dominant strategy (least expensive, highest benefit). For the very elderly patients, older than 85 years, the screen for proteinuria was the dominant intervention.

3. How much does allowance for uncertainty change the results?

Unable to determine. There is considerable impact of uncertainty on results. The cost-utility analysis was sensitive to drug costs, risk of progression of nephropathy and HRQOL estimates. This is not surprising, however, given the wide range of the sensitivity analysis and the wide ranges used.

Will the results help me in caring for my patients?

1. Are the treatment benefits worth the harms and costs?

Yes. The base estimate for the cost of ACE inhibitors used was \$320/yr, which resulted in a cost-effectiveness ratio of \$7500/QALY. There is an incremental cost effectiveness in the treat all category if the cost of the ACE inhibitor is less than \$260/yr. If the annual cost of ACE exceeds \$420/yr, the marginal cost-effectiveness ratio of the treat all strategy exceeds \$20000/QALY. These are all relative values of treating all at the time of diagnosis. Screening for gross proteinuria was more costly and less effective. It was a dominated strategy. The findings in this study were not sensitive to screening adherence or treatment discontinuation. However, if adherence to screening was 100%, and if no patient discontinued treatment, the treat-all strategy was still cost effective.

2. Could my patients expect similar health outcomes?

This study was a model of a hypothetical cohort of type 2 diabetics, based in part on the results of one clinical study conducted on Type 1 diabetics. Like all economic analyses, the results are not relevant to the individual patient, but is relevant for the entire patient population. Nonetheless, the model allows for variation in adherence to screening guidelines and treatment discontinuation, age at diagnosis, costs, different degrees of efficacy of ACE inhibitor therapy, and mortality (lifetime outcomes). The study patients were type 2 diabetics and since an ideal study would require a large number of patients with a long follow-up, this study models such an ideal trial. It accounted for treatment discontinuation but assumed perfect screening as per National guidelines. However, there are new diagnostic criteria for diabetes and the new criteria may allow for earlier diagnosis and therefore improved cost-effectiveness.

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Yes, more or less. Costs seem to have been taken from appropriate "normal" U.S. sources (literature and fee guides) but the model was taken from an American perspective and costs may differ and therefore the results may not be directly relevant. Costs in Canada may differ, and the different provinces in Canada may have different drug costs. This is especially important because the model was shown to be sensitive to drug costs. Therefore, whether or not we could expect similar cost effectiveness depends on the local drug costs. In Alberta, for example, the average wholesale price per year of lisinopril (as used in the study) is \$295.36/yr. This value falls within the range of the sensitivity analysis, and also falls close to the base annual cost used in this study (\$320). Also, the study used 1998 costs of drugs, and 1996 cost for dialysis, but the range of the sensitivity analysis was very wide for costs, so we could therefore expect costs to be in the range of the sensitivity analysis.

How can the results be put into the context of previous knowledge and clinical practice? What are any important methodological issues with the study? How should the study findings be applied to the field of clinical pharmacotherapy?

The results of this study were based on a Markov model of a hypothetical cohort of type 2 diabetic patients. In order for a clinical trial to weigh the costs of treating patients with ACE inhibitors against the progression of nephropathy, a large number of patients with a very long follow-up period would be required, and therefore, the modeling of progression might be the most appropriate type of study. There is limited, but mounting, previous clinical knowledge regarding treatment with ACE inhibitors in type 2 diabetes. The current Canadian clinical practice guidelines recommend that all patients with type 1 or type 2 diabetes be annually screened for microalbuminuria (grade D consensus). (1) The CPGs also recommend treatment with an ACE inhibitor for type 1 diabetics with elevated microalbuminuria (30-299 mg/d) to decrease the albuminuria (grade A consensus). They currently do not recommend treating all type 2 diabetic patients with ACE inhibitors, but suggest that ACE inhibitor treatment may be beneficial (grade B). ACE inhibition is also recommended for type 1 diabetics with overt nephropathy (grade A consensus). The model of this study suggests that all newly diagnosed type 2 diabetic patients should be treated with ACE inhibitors to prevent the progression of nephropathy and that treating all patients would be cost effective. However, CPGs are more conservative since clinical evidence is still lacking and thus cannot provide a strong recommendation with respect to ACE inhibitor

treatment in all diabetic patients.

Reference

1. Meltzer S, Leiter L, Daneman D, Gerstein HC, Lau D, Ludwig S, Yale JF, Zinman B, Lillie D. 1998 clinical practice guidelines for the management of diabetes in Canada. Canadian Diabetes Association. CMAJ 1998;159 Suppl 8:S1-29.

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Cost-effectiveness of treating type 2 diabetes with angiotensin-converting enzyme inhibitors: Should all patients receive this agent?

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Reviewer's profession/specialty: Researchers, Health Outcomes Research, Faculty of Pharmacy & Pharmaceutical Sciences, Institute of Pharmacoeconomics, University of Alberta, Edmonton, Alberta, Canada

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J Inform Pharmacother 2000;2:206-9.

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2000;2:209-211.

Healing NSAID-induced gastric ulcers: have we found the optimal antisecretory agent?

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Reviewers_Specialty: Pharmacy/Emergency Medicine

Original Citation

Agrawal NM, Campbell DR, Safdi MA, Lukasik NL, Huang B, Haber MM for the NSAID-Associated Gastric Ulcer Study Group. Superiority of lansoprazole vs. ranitidine in healing non-steroidal anti-inflammatory drug-induced gastric ulcers. *Arch Intern Med* 2000;160:1455-61. [PubMed Citation](#)

Overall Study Question

This study was a prospective, multicentre, double-blind, parallel group study designed to identify the optimal antisecretory therapy for healing of gastric ulcers in patients using an nonsteroidal anti-inflammatory drug (NSAID) and the impact of *Helicobacter pylori* infection on gastric ulcer healing.

Patients aged 18 years or older with an active non-malignant gastric ulcer (primary lesions >5 mm in diameter) documented by endoscopic and biopsy findings and who were receiving a stable dose of an NSAID for at least the previous month were eligible for enrollment into the study. The primary study endpoint was gastric ulcer healing rate at 8 weeks. Secondary endpoints included gastric ulcer healing rate at 8 weeks in *H. pylori*-infected and non-infected patients. Patient symptoms were also assessed using a patient diary that was completed on a daily basis.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. All patients were assigned randomly in a 1:1:1 ratio to receive ranitidine 150 mg orally twice daily, or lansoprazole 15 or 30 mg orally once daily for 8 weeks.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. Endoscopy was performed on 669 patients of which 353 met study criteria for presence of a gastric ulcer and were randomized to received ranitidine 150 mg twice daily (n=117), lansoprazole 15 mg daily (n=119) or lansoprazole 30 mg daily (n=117). Three patients were excluded from all efficacy analysis (2 patients had no gastric ulcer and one patient did not receive an NSAID before and during treatment). In addition, 9 patients were not included in the analysis of patient diary data because they did not record data.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. A double-dummy blind design was used to maintain the double-blind nature of the study. Patients administered one capsule before breakfast and dinner for 8 weeks.

4. Were the groups similar at the start of the trial?

Yes. All three groups demonstrated similar baseline parameters at the start of the trial.

5. Aside from the experimental intervention, were the groups treated equally?

Yes. Patients also received antacid tablets (400 mg each of aluminum hydroxide and magnesium hydroxide and 25 mg of simethicone) and were instructed only to use them for symptom relief as needed. Patients were also instructed to avoid any other antiulcer (e. g. H₂-receptor antagonist, > misoprostol, or sucralfate) or ulcerogenic medications (except an NSAID or low dose aspirin) other than the study medications until completion of the study.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

The primary endpoint, gastric ulcer healing at 8 weeks, occurred in 53% patients treated with ranitidine compared to 69% of patients who received lansoprazole 15 mg (p=0.01 vs. ranitidine, 95% confidence interval [CI] for the difference between groups 3.2-28.0) and 73% of patients who received lansoprazole 30 mg, (p=0.009 vs. ranitidine, 95% CI 7.4-31.8). This correlates to an absolute risk reduction (ARR) of 16-20% and a number needed

to treat of 5 and 7 for lansoprazole 15 and 30 mg daily, respectively, as compared to ranitidine for ulcer healing at 8 weeks.

The secondary endpoint of gastric ulcer healing rate at 8 weeks in H. pylori-infected and non-infected patients was not different between the groups. As with the total population, the lansoprazole 15 mg and 30 mg recipients had higher gastric ulcer healing rates at 8 weeks in both the H. pylori-infected (67% and 82%, respectively) and non-infected patients (70% and 69%, respectively) as compared to ranitidine (60% and 51% for H. pylori positive and negative patients, respectively).

During the 8 treatment weeks, there was no difference in the improvement in symptom relief, however a statistically significant reduction in antacid use was observed with lansoprazole 15 mg ($p<0.01$) and 30 mg ($p<0.05$) use as compared to ranitidine. In particular, there were fewer antacid tablets per day (ranitidine 1.11 vs. lansoprazole 15 mg 0.86 ($p<0.05$) vs. lansoprazole 30 mg 0.78 ($p<0.01$)) and a smaller percentage of days of antacid use (ranitidine 35.6% vs. lansoprazole 15 mg 30.9% ($p=ns$) vs. lansoprazole 30 mg 28.7% ($p<0.05$)). The authors did not provide information regarding any actual OTC use of H₂-receptor antagonists or other medications.

Overall, treatment-related adverse effects occurred in 11% of ranitidine-treated patients and 8% and 9% of lansoprazole 15 mg and 30 mg recipients, respectively. The most common adverse effect reported by the patients was diarrhea. There were no statistically significant differences among treatment groups for any specific drug-related adverse effect.

2. How precise was the estimate of the treatment effect?

The 95% CI for the primary endpoint of gastric ulcer healing at 8 weeks did not include zero, thus indicating statistical significance. In this author's opinion, the lower end of the CI range still represents a clinically significant difference between treatment groups.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. The results of this trial can be applied to the care of patients as the data provides additional evidence that proton-pump inhibitors (PPI) appear to be the agents of choice for the treatment of NSAID-induced gastric ulcers. Prior to this trial, omeprazole was the only agent that has been shown to improve gastric ulcer healing and prevent NSAID-induced gastric ulcers. With the additional information from this trial, the use of lansoprazole brings up the question of whether a class effect for the PPI exists for this indication. Clearly, the use of lansoprazole is superior to ranitidine for this indication.

2. Were all clinically important outcomes considered?

Yes, although health-related quality of life and pharmacoeconomic analyses would have been useful.

3. Are the likely treatment benefits worth the potential harms and costs?

Probably.

Commentary

This clinical trial adds to the growing body of evidence that PPI are the antisecretory agents of choice in the treatment and prevention of NSAID-induced gastric ulcer disease regardless of H. pylori status. The ASTRONAUT trial (1) has established that omeprazole appears to be superior to ranitidine in healing both gastric and duodenal ulcers at 8 weeks and for the maintenance of remission at 6 months for NSAID-induced gastric ulcer disease in patients who continue NSAID therapy for a primary inflammatory disorder. The OMNIUM trial (2) has demonstrated that omeprazole appears to be as effective as misoprostol in healing ulcers at 8 weeks, but is superior at maintaining remission at 6 months. The addition of the results of the current trial confirms these findings and supports the use of PPI for both the treatment and prevention of NSAID-induced gastric ulcers.

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Healing NSAID-induced gastric ulcer disease: have we found the optimal antisecretory agent?

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Reviewers Email: zed@interchange.ubc.ca

Reviewers Specialty: Pharmacy/Emergency Medicine, Vancouver Hospital and Health Sciences Centre, Vancouver, B.C., Canada.

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Yes.

What were the Results?

1. How large was the treatment effect?

The primary endpoint, gastric ulcer healing at 8 weeks, occurred in 53% patients treated with ranitidine compared to 69% of patients who received lansoprazole 15 mg ($p=0.01$ vs. ranitidine, 95% confidence interval [CI] for the difference between groups 3.2-28.0) and 73% of patients who received lansoprazole 30 mg, ($p=0.009$ vs. ranitidine, 95% CI 7.4-31.8). This correlates to an absolute risk

reduction (ARR) of 16-20% and a number needed to treat of 5 and 7 for lansoprazole 15 and 30 mg daily, respectively, as compared to ranitidine for ulcer healing at 8 weeks.

The secondary endpoint of gastric ulcer healing rate at 8 weeks in *H. pylori*-infected and non-infected patients was not different between the groups. As with the total population, the lansoprazole 15 mg and 30 mg recipients had higher gastric ulcer healing rates at 8 weeks in both the *H. pylori*-infected (67% and 82%, respectively) and non-infected patients (70% and 69%, respectively) as compared to ranitidine (60% and 51% for *H. pylori* positive and negative patients, respectively).

During the 8 treatment weeks, there was no difference in the improvement in symptom relief, however a statistically significant reduction in antacid use was observed with lansoprazole 15 mg ($p<0.01$) and 30 mg ($p<0.05$) use as compared to ranitidine. In particular, there were fewer antacid tablets per day (ranitidine 1.11 vs. lansoprazole 15 mg 0.86 ($p<0.05$) vs. lansoprazole 30 mg 0.78 ($p<0.01$)) and a smaller percentage of days of antacid use (ranitidine 35.6% vs. lansoprazole 15 mg 30.9% ($p=ns$) vs. lansoprazole 30 mg 28.7% ($p<0.05$)). The authors did not provide information regarding any actual OTC use of H₂-receptor antagonists or other medications.

Overall, treatment-related adverse effects occurred in 11% of ranitidine-treated patients and 8% and 9% of lansoprazole 15 mg and 30 mg recipients, respectively. The most common adverse effect reported by the patients was diarrhea. There were no statistically significant differences among treatment groups for any specific drug-related adverse effect.

2. How precise was the estimate of the treatment effect?

The 95% CI for the primary endpoint of gastric ulcer healing at 8 weeks did not include zero, thus indicating statistical significance. In this author's opinion, the lower end of the CI range still represents

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a clinically significant difference between treatment groups.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. The results of this trial can be applied to the care of patients as the data provides additional evidence that proton-pump inhibitors (PPI) appear to be the agents of choice for the treatment of NSAID-induced gastric ulcers. Prior to this trial, omeprazole was the only agent that has been shown to improve gastric ulcer healing and prevent NSAID-induced gastric ulcers. With the additional information from this trial, the use of lansoprazole brings up the question of whether a class effect for the PPI exists for this indication. Clearly, the use of lansoprazole is superior to ranitidine for this indication.

2. Were all clinically important outcomes considered?

Yes, although health-related quality of life and pharmacoeconomic analyses would have been useful.

3. Are the likely treatment benefits worth the potential harms and costs?

Probably.

Commentary

This clinical trial adds to the growing body of evidence that PPI are the antisecretory agents of choice in the treatment and prevention of NSAID-induced gastric ulcer disease regardless of *H. pylori* status. The ASTRONAUT trial (1) has established that omeprazole appears to be superior to ranitidine in healing both

gastric and duodenal ulcers at 8 weeks and for the maintenance of remission at 6 months for NSAID-induced gastric ulcer disease in patients who continue NSAID therapy for a primary inflammatory disorder. The OMNIUM trial (2) has demonstrated that omeprazole appears to be as effective as misoprostol in healing ulcers at 8 weeks, but is superior at maintaining remission at 6 months. The addition of the results of the current trial confirms these findings and supports the use of PPI for both the treatment and prevention of NSAID-induced gastric ulcers.

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J Inform Pharmacother 2000;2:209-211

Issues in Pharmacotherapy Practice

Combination Antipsychotics: What is the Evidence?

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Abstract

Objective: To identify clinical situations where combination antipsychotic drug therapies are used, and to review the evidence supporting the use of such combinations.

Methods: MEDLINE (1966-April 2000), Cochrane Library and EMBASE (1980-April 2000) searches were performed to identify literature pertinent to the practice of combining antipsychotics. Articles selected included clinical trials, anecdotal reports and discussion papers pertaining to antipsychotic augmentation or combination therapy. Key words used in the search were *antipsychotic*, *neuroleptic*, *combination* and *augmentation*.

Results: Examples where combination antipsychotics are used include: the augmentation of clozapine for partially or non-responsive patients; the addition of a traditional antipsychotic to an atypical agent; the short-term co-administration of traditional agents when initiating therapy with a novel antipsychotic; and as a result of an incomplete switchover from one antipsychotic to another. Despite the commonality of such practices, only one randomized controlled trial could be identified which involved the addition of sulpiride (a potent D2 antagonist) to clozapine. The remaining indexed literature was comprised of two open, prospective trials, a single retrospective review and four separate anecdotal reports.

Conclusion: Clinicians are advised to evaluate the rationale for combining antipsychotics before doing so as there is a paucity of published evidence to support such practices. Combination antipsychotic therapy can potentially lead to more complex, less well-tolerated treatment regimens that may reduce patient compliance and increase treatment costs.

J Inform Pharmacother 2000;2:300-305.

Introduction

Combination antipsychotic use or the practice of augmenting the use of one antipsychotic

with another is a common clinical scenario. The potential disadvantages of combining antipsychotics include: increased risk of adverse effects; increased risk of noncompliance; and increased drug costs. The frequent use of combination antipsychotic therapy may stem from the perceived slow onset of action of the novel agents and the need for quick recoveries in a system under pressure to shorten or avoid hospital inpatient stays. Presumed enhanced efficacy when using agents with dissimilar pharmacologies may also lead some clinicians to trial combined regimens for patients who are partially or completely unresponsive to monotherapy. Because of the potential disadvantages of combining antipsychotics, evidence for improved efficacy of combination therapy over single agents is required. Accordingly, the description of clinical situations where combinations of antipsychotics may be used and assessment of published evidence to support such practices was sought out. Thus, the objective of this paper is to identify clinical situations where combination antipsychotic drug therapies are used, and to review the evidence supporting the use of such combinations.

Methodology

A literature search using MEDLINE (1966-April 2000), Cochrane Library and EMBASE (1980-April 2000) was performed to identify literature pertinent to the practice of combining antipsychotics. Articles selected included clinical trials, anecdotal reports and discussion papers pertaining to antipsychotic augmentation or combination therapy. Key words used in the search were *antipsychotic*, *neuroleptic*, *combination* and *augmentation*.

Results

Only one randomized controlled trial could be identified while the remaining indexed literature was comprised of two open, prospective trials, a single retrospective review and four separate anecdotal reports (Table 1).

Clozapine Augmentation: A Controlled Clinical Trial

At present, the bulk of published data on combining antipsychotics involves clozapine. Typically, clozapine is relegated to last resort therapy due to the risk of agranulocytosis and the requirement for regular blood monitoring. (1) Approximately 30-60% of patients resistant to previous antipsychotic trials respond to clozapine monotherapy. (2) While there is no clear consensus on how to manage patients whose symptoms persist despite an adequate course of clozapine, the results of a study by Shiloh et al (3) suggest a possible role for sulpiride, a selective D2 antagonist. (3) In this double-blind, placebo-controlled study, 28 patients with schizophrenia who had partial or unsatisfactory responses to clozapine at adequate doses for at least 12 weeks were randomized to receive additional therapy with either sulpiride or placebo for a period of 10 weeks. The investigators reported that Brief Psychiatric Rating Scale (BPRS) scores were reduced by 8.7 points (20.7%) in the sulpiride group versus 2.3 points (5.4%) in the placebo group ($p < 0.05$). The between group differences in positive and negative symptom score reductions were reported to be 5.8 points (12.3%) and 6.8 points (10.4%), respectively, in favour of sulpiride ($p < 0.05$). There was a trend toward younger patients exhibiting a greater than 20% reduction in BPRS scores (35.3 versus 45.4 years), suggesting that a subgroup of patients with chronic schizophrenia may obtain significant benefits from this combination. Overall, the combination of clozapine and sulpiride was well tolerated with

the exception of hyperprolactinemia. There was a 4- to 7-fold increase noted in the serum prolactin levels of the sulpiride-treated subjects ($p < 0.05$) while no changes were observed in the clozapine+placebo group. Despite this, none of the 5 female patients with hyperprolactinemia complained of galactorrhea and 3 of the 5 were amenorrheic prior to enrollment in the trial and remained so for the duration of the study. This side effect did not result in an alteration in treatment.

A limitation of this study was a statistically significant difference in previous total duration of hospitalization between the 2 groups, with patients in the placebo arm (70.8 $\pm$ 56.1 months) experiencing a mean pre-trial hospitalization period that was twice the duration of that reported for the study group (32.8 $\pm$ 30.3 months) ($p < 0.05$). These investigators address the implications of this limitation; however, they point out that this difference was not reflected in the clinical status of the patients at baseline. Other limitations of this study included a small sample size, the exclusion of complete nonresponders to clozapine and limited study duration of only 10 weeks. Continued clinical improvement with clozapine therapy may be seen after 12-24 months of treatment. (1) Thus, it is not clear whether the patients would have improved with clozapine alone or if sulpiride contributed to the overall improvement. Albeit encouraging, validation of these results by other investigators and with other potent D2 antagonists is needed to support this treatment approach.

Clozapine Augmentation: Uncontrolled Clinical Trials

In 1997, Friedman published a case series involving augmentation of clozapine with pimozide, another potent D2 antagonist. (4) Although this was not a controlled trial, the results were also positive and consistent with the sulpiride trial described above. (3) Pimozide, at doses ranging from 2-8 mg/day, was added to clozapine in 7 patients previously diagnosed with either schizophrenia or schizoaffective disorder. These patients had been receiving treatment with clozapine for at least 10 months prior to the addition of pimozide, and were considered to be only partial responders. The mean change in BPRS score was 24 points (24%) ($p = 0.003$) over an average treatment period of 32 days. Unfortunately, the authors did not describe how well the combination was tolerated by these patients and it is unclear whether any of these patients continued with both clozapine and pimozide, as a consequence of the favourable results. While the limitations of this report are quite apparent, the case series does provide an impetus for future studies.

Possibly more compelling are "open trial publications" on the augmentation of clozapine with risperidone and loxapine both describing favourable effects. (5,6) The risperidone group consisted of 12 patients with either schizophrenia or schizoaffective disorder who had persistent psychotic symptoms after at least 12 months of clozapine therapy. Patients received 4 weeks of treatment with risperidone up to a maximum dose of 6 mg/day. The mean reduction in total BPRS scores was 11.9 points (28%) ($p = 0.0002$) and 10 of the 12 patients showed a greater than 20% reduction in such scores. Risperidone did not seem to have significant effects on clozapine disposition as evidenced by clozapine levels drawn at baseline and at the end of the 4 weeks. (5)

Loxapine was added to clozapine in an open 18-50 week trial with 7 patients diagnosed with schizophrenia or schizoaffective disorder, who had previous treatment with clozapine for at least 9 months. All patients were concurrently attending a structured day hospital program, which may have contributed to their improvement and confounded the results. A 19-38 point reduction in BPRS scores was reported, with 2 patients described as being "rapid responders", with improvement demonstrated within 3 weeks of initiating loxapine. Clozapine serum levels were not significantly altered by the addition of loxapine as monitored in 4 of the 7 patients. Unfortunately, little information

was provided regarding reported adverse effects with this group other than the authors declaration that no serious effects were observed. (6)

Clozapine Augmentation: Anecdotal Reports

Finally, two anecdotal reports were identified describing augmentation of clozapine with either olanzapine or risperidone. (7,8) Gupta et al. report success with the addition of olanzapine to clozapine in 2 patients; however, the length of clozapine trial prior to the addition of olanzapine was not indicated. (7) One patient was reported to have a 35% improvement in symptoms and the second a 13-point reduction in BPRS score. The only adverse effect identified was a case of drooling in one patient. The investigators stated that neither patient had significant extrapyramidal side effects or orthostatic hypotension with this combination. In a report by McCarthy and Terkelsen, the augmentation of clozapine with risperidone in 2 patients whose clozapine dose was limited due to intolerable adverse effects, was described as successful. (8) Again, the length of clozapine trial prior to the addition of risperidone was unclear and tolerance to the combination was not specified. The benefits of these regimens remain inconclusive because of small sample sizes, lack of a control group and the likelihood of publication bias (i.e. lack of publication of negative trials of the above combinations).

Other Antipsychotic Combinations

Possibly more prevalent is the practice of augmenting antipsychotics other than clozapine. Anecdotal reports of adding a conventional antipsychotic to a novel agent exist however, scarce. Waring and colleagues describe success with using this strategy in 31 refractory schizophrenic patients over a 9-month review period, and proposed that this approach could be an alternative to using clozapine. (9) These authors report using low dose haloperidol, trifluoperazine or fluphenazine in conjunction with risperidone, olanzapine or quetiapine. Unfortunately, details of the specific combinations used were not reported. Two-thirds of these patients were reported to have improved and were discharged from hospital. Little information is provided by the authors regarding patient tolerance to the combinations other than noting the absence of serious adverse effects.

Takhar reported improvement after 7 weeks of pimozone 2 mg/day augmentation of olanzapine in a patient exhibiting residual psychotic symptoms despite 6 months of treatment with olanzapine 20 mg/day. (10) The patient was noted to have had a BPRS score reduction of 18 points (32%). Tolerability of this regimen is not discussed other than the patient did not display evidence of tardive dyskinesia. Although, provocative, these case reports suffer the same limitations as the anecdotal reports involving cocaine combinations.

Other Combination Antipsychotic Use

A related scenario to the aforementioned is the short-term administration of conventional agents when initiating therapy with a second-generation antipsychotic. This has become commonplace at some centres because of the belief that the novel agents are not as effective for treating agitation and aggression that often accompany acute psychosis. (1,12) Unpublished data from a retrospective analysis of two acute admitting units revealed that concomitant haloperidol use was highest with quetiapine and lowest with

risperidone, supporting the impression that clinicians lack confidence in the new agents for inpatient treatment or possibly the inefficacy of quetiapine. (12) The pharmacologic hypothesis appears to be that potent D2 blockade is required for resolution of acute psychotic episodes. (12) Thus, quetiapine, a weak D2 blocker, would require augmentation with haloperidol, unlike risperidone, a potent D2 blocker. (1,11,12) If this is employed, it is important to regularly reassess the need for both medications in order to minimize extrapyramidal side effects and ineffective polypharmacy.

Other cases of combination antipsychotic use occur when patients are being switched from one agent to another because of poor response or tolerance. Most often the two therapies are overlapped and if a patient shows improvement during the cross-titration, there may be reluctance to make subsequent changes. This practice is generally discouraged due to the potential for increased costs, noncompliance and reduced tolerability, and is not supported by published evidence. (11,15)

Table 1: Clinical trials and anecdotal reports regarding the use of combination antipsychotics.

Trial	Design/N	Treatment Arms/ (N/N)	Results (Mean Reduction in BPRS* Scores)	Adverse Effects
Shiloh et al. 1997	RCT**/28	Clozapine + Sulpiride (16) Clozapine + Placebo (12)	8.7 points (20.7%) vs. 2.3 points (5.4%) in favour of sulpiride addition (p<0.05)	4-7-fold increase in serum prolactin levels.
Friedman et al. 1997	Retrospective review/7	Clozapine + Pimozide	24 points (47%) (p=0.003)	Not reported.
Henderson et al. 1996	Open prospective trial/12	Clozapine + Risperidone	11.9 points (28%)	Mild akathisia reported in 4 patients and return of hypersalivation in 1 patient.
Mowerman et al. 1996	Open prospective trial/7	Clozapine + Loxapine	19-38 points	No serious adverse effects reported.

Gupta et al. 1998	Case reports/2	Clozapine + Olanzapine	13 point reduction for 1 patient and a 35% improvement in the second (not specified)	Drooling described in 1 patient.
McCarthy et al. 1995	Case reports/2	Clozapine + Risperidone	Not specified. Authors report improvement in both patients.	Not reported.
Waring et al. 1999	Case reports/31	Conventional + Novel (haloperidol, trifluoperazine, and fluphenazine with risperidone, olanzapine and quetiapine)	Not specified. Authors report clinical improvement in 2/3 of patients.	No serious adverse effects and a few “unpleasant subjective” side effects reported.
Takhar 1999	Case report/1	Olanzapine + Pimozide	18 points (32%)	No discussion of adverse effects.

*BPRS= Brief Psychiatric Rating Scale

**RCT=randomized controlled trial

Discussion

Not addressed by these reports is an evaluation of the trade-offs among benefits, safety and costs when combining antipsychotics. Early experience with the novel agents indicated a more appealing adverse effect profile, primarily due to a reduction in the risk for extrapyramidal side effects and tardive dyskinesia. However, as experience accumulates new risks associated with the novel agents have attracted concern, including obesity, diabetes (including diabetic ketoacidosis), hepatic dysfunction, and most recently cardiomyopathy. (13,14) When traditional and novel antipsychotics are combined, patients are put at risk simultaneously for both the *old* and *new* adverse effects. The question remains, and will continue until long-term, controlled data becomes available, whether the benefits of combination antipsychotics are worth the risks to health and budget.

Before considering combining antipsychotics, clinicians should first examine the reasons for doing so. The addition of a second antipsychotic to clozapine-resistant patients is considered an appropriate intervention, as there is yet no other treatment shown to be as or more effective than clozapine for this patient population. The strongest evidence for such an approach, however limited at this time, is for sulpiride. Unfortunately, sulpiride's

availability is, at present, restricted and in Canada can only be obtained through Health Canada's special access program. (16) The United States does not have a similar program for sulpiride and as such is not available. Thus, further controlled studies are required to determine whether or not the same gains can be made by substituting other potent antipsychotics for sulpiride (e.g., pimozide, haloperidol). The augmentation of the second-generation agents with a conventional agent is generally discouraged due to lack of evidence and risk for increased adverse effects, cost and noncompliance. Patients should be given adequate treatment trials and if poor response is observed, clozapine should be considered. The practice of using "prn" doses of conventional antipsychotics during initiation of a second-generation agent is thought to be a rational approach for acute psychotic episodes when agitation or aggression is present. Clinicians should; however, assess whether benzodiazepines would be a more appropriate choice in these cases. Finally, combination antipsychotic use as a result of incomplete cross-titration is not recommended. Instead, switching should always be completed to allow for proper assessment of the new agent.

Acknowledgement

I would like to acknowledge David M. Gardner, Pharm.D., Department of Psychiatry, Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada for his invaluable contributions and editing of this article.

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Results: Examples where combination antipsychotics are used include: the augmentation of clozapine for partially or non-responsive patients; the addition of a traditional antipsychotic to an atypical agent; the short-term co-administration of traditional agents when initiating therapy with a novel antipsychotic; and as a result of an incomplete switchover from one antipsychotic to another. Despite the commonality of such practices, only one randomized controlled trial could be identified which involved the addition of sulpiride (a potent D2 antagonist) to clozapine. The remaining indexed literature was comprised of two open, prospective trials, a single retrospective review and four separate anecdotal reports.

Conclusion: Clinicians are advised to evaluate the rationale for combining antipsychotics before doing so as there is a paucity of published evidence to support such practices. Combination antipsychotic therapy can potentially lead to more complex, less well-tolerated treatment regimens that may reduce patient compliance and increase treatment costs.

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Combination antipsychotic use or the practice of augmenting the use of one antipsychotic with another is a common clinical scenario. The potential disadvantages of combining antipsychotics include: increased risk of adverse effects; increased risk of noncompliance; and increased drug costs. The frequent use of combination antipsychotic therapy may stem from the perceived slow onset of action of the novel agents and the need for quick recoveries in a system under pressure to shorten or avoid hospital inpatient stays. Presumed enhanced efficacy when using agents with dissimilar pharmacologies may also lead some clinicians to trial combined regimens for patients who are partially or completely unresponsive to monotherapy. Because of the potential disadvantages of combining antipsychotics, evidence for improved efficacy of combination therapy over single agents is required. Accordingly, the description of clinical situations where combinations of antipsychotics may be used and assessment of published evidence to support such practices was sought out. Thus, the objective of this paper is to identify clinical situations where combination antipsychotic drug therapies are used, and to review the evidence supporting the use of such combinations.

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At present, the bulk of published data on combining antipsychotics involves clozapine. Typically, clozapine is relegated to last resort therapy due to the risk of agranulocytosis and the requirement for regular blood monitoring. (1) Approximately 30-60% of patients resistant to previous antipsychotic trials respond to clozapine monotherapy. (2) While there is no clear consensus on how to manage patients whose symptoms persist despite an adequate course of clozapine, the results of a study by Shiloh et al (3) suggest a possible role for sulpiride, a selective D2 antagonist. (3) In this double-blind, placebo-controlled study, 28 patients with schizophrenia who had partial or unsatisfactory responses to clozapine at adequate doses for at least 12 weeks were randomized to receive additional therapy with either sulpiride or placebo for a period of 10 weeks. The investigators reported that Brief Psychiatric Rating Scale (BPRS) scores were reduced by 8.7 points (20.7%) in the sulpiride group versus 2.3 points (5.4%) in the placebo group ($p < 0.05$). The between group differences in positive and negative symptom score reductions were reported to be 5.8 points (12.3%) and 6.8 points (10.4%), respectively, in favour of sulpiride ($p < 0.05$). There was a trend toward younger patients exhibiting a greater than 20% reduction in BPRS scores (35.3 versus 45.4 years), suggesting that a subgroup of patients with chronic schizophrenia may obtain significant benefits from this combination. Overall, the combination of clozapine and sulpiride was well tolerated with the exception of hyperprolactinemia. There was a 4- to 7-fold increase noted in the serum prolactin levels of the sulpiride-treated subjects ($p < 0.05$) while no changes were observed in the clozapine+placebo group. Despite this, none of the 5 female patients with hyperprolactinemia complained

of galactorrhea and 3 of the 5 were amenorrheic prior to enrollment in the trial and remained so for the duration of the study. This side effect did not result in an alteration in treatment.

A limitation of this study was a statistically significant difference in previous total duration of hospitalization between the 2 groups, with patients in the placebo arm (70.8 +/- 56.1 months) experiencing a mean pre-trial hospitalization period that was twice the duration of that reported for the study group (32.8 +/- 30.3 months) ($p < 0.05$). These investigators address the implications of this limitation; however, they point out that this difference was not reflected in the clinical status of the patients at baseline. Other limitations of this study included a small sample size, the exclusion of complete nonresponders to clozapine and limited study duration of only 10 weeks. Continued clinical improvement with clozapine therapy may be seen after 12-24 months of treatment. (1) Thus, it is not clear whether the patients would have improved with clozapine alone or if sulpiride contributed to the overall improvement. Albeit encouraging, validation of these results by other investigators and with other potent D2 antagonists is needed to support this treatment approach.

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extrapyramidal side effects or orthostatic hypotension with this combination. In a report by McCarthy and Terkelsen, the augmentation of clozapine with risperidone in 2 patients whose clozapine dose was limited due to intolerable adverse effects, was described as successful. (8) Again, the length of clozapine trial prior to the addition of risperidone was unclear and tolerance to the combination was not specified. The benefits of these regimens remain inconclusive because of small sample sizes, lack of a control group and the likelihood of publication bias (i.e. lack of publication of negative trials of the above combinations).

Other Antipsychotic Combinations

Possibly more prevalent is the practice of augmenting antipsychotics other than clozapine. Anecdotal reports of adding a conventional antipsychotic to a novel agent exist however, scarce. Waring and colleagues describe success with using this strategy in 31 refractory schizophrenic patients over a 9-month review period, and proposed that this approach could be an alternative to using clozapine. (9) These authors report using low dose haloperidol, trifluoperazine or fluphenazine in conjunction with risperidone, olanzapine or quetiapine. Unfortunately, details of the specific combinations used were not reported. Two-thirds of these patients were reported to have improved and were discharged from hospital. Little information is provided by the authors regarding patient tolerance to the combinations other than noting the absence of serious adverse effects.

Takhar reported improvement after 7 weeks of pimozone 2 mg/day augmentation of olanzapine in a patient exhibiting residual psychotic symptoms despite 6 months of treatment with olanzapine 20 mg/day. (10) The patient was noted to have had a BPRS score reduction of 18 points (32%). Tolerability of this regimen is not discussed other than the patient did not display evidence of tardive dyskinesia. Although provocative, these case reports suffer the same limitations as the anecdotal reports involving clozapine combinations.

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Table 1: Clinical trials and anecdotal reports regarding the use of combination antipsychotics.

Trial	Design/N	Treatment Arms/ (N/N)	Results (Mean Reduction in BPRS* Scores)	Adverse Effects
Shiloh et al. 1997	RCT**/28	Clozapine + Sulpiride (16) Clozapine + Placebo (12)	8.7 points (20.7%) vs. 2.3 points (5.4%) in favour of sulpiride addition (p<0.05)	4-7-fold increase in serum prolactin levels.
Friedman et al. 1997	Retrospective review/7	Clozapine + Pimozide	24 points (47%) (p=0.003)	Not reported.
Henderson et al. 1996	Open prospective trial/12	Clozapine + Risperidone	11.9 points (28%)	Mild akathisia reported in 4 patients and return of hypersalivation in 1 patient.
Mowerman et al. 1996	Open prospective trial/7	Clozapine + Loxapine	19-38 points	No serious adverse effects reported.
Gupta et al. 1998	Case reports/2	Clozapine + Olanzapine	13 point reduction for 1 patient and a 35% improvement in the second (not specified)	Drooling described in 1 patient.
McCarthy et al. 1995	Case reports/2	Clozapine + Risperidone	Not specified. Authors report improvement in both patients.	Not reported.
Waring et al. 1999	Case reports/31	Conventional + Novel (haloperidol, trifluoperazine, and fluphenazine with risperidone, olanzapine and quetiapine)	Not specified. Authors report clinical improvement in 2/3 of patients.	No serious adverse effects and a few "unpleasant subjective" side effects reported.
Takhar 1999	Case report/1	Olanzapine + Pimozide	18 points (32%)	No discussion of adverse effects.

*BPRS= Brief Psychiatric Rating Scale

**RCT=randomized controlled trial

Other Antipsychotic Combination Use

A related scenario to the aforementioned is the short-term administration of conventional agents when initiating therapy with a second-generation antipsychotic. This has become commonplace at some centres because of the belief that the novel agents are not as effective for treating agitation and aggression that often accompany acute psychosis. (1,12) Unpublished data from a retrospective analysis of two acute admitting units revealed that concomitant haloperidol use was highest with quetiapine and lowest with risperidone, supporting the impression that clinicians lack confidence in the new agents for inpatient treatment or possibly the inefficacy of quetiapine. (12)

The pharmacologic hypothesis appears to be that potent D2 blockade is required for resolution of acute psychotic episodes. (12) Thus, quetiapine, a weak D2 blocker, would require augmentation with haloperidol, unlike risperidone, a potent D2 blocker. (1,11,12) If this is employed, it is important to regularly reassess the need for both medications in order to minimize extrapyramidal side effects and ineffective polypharmacy.

Other cases of combination antipsychotic use occur when patients are being switched from one agent to another because of poor response or tolerance. Most often the two therapies are overlapped and if a patient shows improvement during the cross-titration, there may be reluctance to make subsequent changes. This practice is generally discouraged due to

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the potential for increased costs, noncompliance and reduced tolerability, and is not supported by published evidence. (11,15)

Discussion

Not addressed by these reports is an evaluation of the trade-offs among benefits, safety and costs when combining antipsychotics. Early experience with the novel agents indicated a more appealing adverse effect profile, primarily due to a reduction in the risk for extrapyramidal side effects and tardive dyskinesia. However, as experience accumulates new risks associated with the novel agents have attracted concern, including obesity, diabetes (including diabetic ketoacidosis), hepatic dysfunction, and most recently cardiomyopathy. (13,14) When traditional and novel antipsychotics are combined, patients are put at risk simultaneously for both the *old* and *new* adverse effects. The question remains, and will continue until long-term, controlled data becomes available, whether the benefits of combination antipsychotics are worth the risks to health and budget.

Before considering combining antipsychotics, clinicians should first examine the reasons for doing so. The addition of a second antipsychotic to clozapine-resistant patients is considered an appropriate intervention, as there is yet no other treatment shown to be as or more effective than clozapine for this patient population. The strongest evidence for such an approach, however limited at this time, is for sulpiride. Unfortunately, sulpiride's availability is, at present, restricted and in Canada can only be obtained through Health Canada's special access program. (16) The United States does not have a similar program for sulpiride and as such is not available. Thus, further controlled studies are required to determine whether or not the same gains can be made by substituting other potent antipsychotics for sulpiride (e.g., pimozide, haloperidol). The augmentation of the second-generation agents with a conventional agent is generally discouraged due to lack of evidence and risk for increased adverse effects, cost and noncompliance. Patients should be given adequate treatment trials and if poor response is observed, clozapine should be considered. The practice of using "prn" doses of conventional antipsychotics during

initiation of a second-generation agent is thought to be a rational approach for acute psychotic episodes when agitation or aggression is present. Clinicians should; however, assess whether benzodiazepines would be a more appropriate choice in these cases. Finally, combination antipsychotic use as a result of incomplete cross-titration is not recommended. Instead, switching should always be completed to allow for proper assessment of the new agent.

Acknowledgement

I would like to acknowledge David M. Gardner, Pharm.D., Department of Psychiatry, Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada for his invaluable contributions and editing of this article.

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Issues in Pharmacotherapy Practice

Is Coronary Artery Disease an Infectious Disease?

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Abstract

Established risk factors for coronary artery disease (CAD) such as elevated serum lipids, smoking, hypertension, diabetes, age, gender, and family history are estimated to account for less than half the prevalence and severity of CAD. In searching for additional risk factors, the potential role of infection in the pathogenesis of atherosclerosis has received increasing attention. Based on the evidence from seroepidemiological studies, *Chlamydia pneumoniae* has emerged as the organism with the strongest apparent relationship with CAD. The first serological evidence emerged in 1988. Since then, several more studies have established the prevalence of this organism in patients with CAD. Histopathological studies have provided more direct evidence of *C. pneumoniae* in atherosclerotic lesions. However, despite evidence of its presence in patients with CAD, the significance of this association and whether or not the organism contributes to the progression and complications of the disease are unknown. Although several mechanisms by which *C. pneumoniae* may contribute to atherosclerosis have been postulated, the hypothesis that this organism contributes to inflammation in atherosclerosis has resulted in clinical trials of antichlamydial antibiotics in CAD patients. The results of the three trials completed to date have been inconclusive. Further evidence is required to establish the role of antibiotics in CAD. Currently, large secondary prevention trials are under way (WIZARD and ACES) which should help to elucidate whether *C. pneumoniae* plays a role in the etiology of atherosclerosis and its complications.

J Inform Pharmacother 2000;2:320-325.

Introduction

Atherosclerosis, the pathological basis for coronary heart disease, is highly prevalent in Western society and a major cause of mortality. (1) Established risk factors for coronary artery disease (CAD) such as elevated serum lipids, smoking, hypertension, diabetes, age, gender, and family history are estimated to account for less than half the prevalence and severity of CAD. (2) Many of the attributable risks for this disease remain unknown. In the search for additional risk factors, the potential role of infection in the pathogenesis

of atherosclerosis has received recent attention. (1-13)

Several organisms have been studied to determine a potential relationship with CAD. The organisms most often implicated include herpes viruses (particularly cytomegalovirus), *Helicobacter pylori* and *C. pneumoniae*. (3) Based on seroepidemiologic and histopathologic evidence, *C. pneumoniae*, has emerged as the pathogen that appears to have the strongest apparent relationship. *C. pneumoniae* is a gram-negative obligatory intracellular bacteria responsible for a wide range of chronic, progressive, inflammatory conditions and is widely recognized as an important cause of respiratory tract infections. (4) This article will provide a brief overview of the evidence for *C. pneumoniae* in CAD and the preliminary evidence for the role of antibiotics in CAD.

Seroepidemiology

Many seroepidemiological studies have been completed over the past decade that provide evidence for an association between *C. pneumoniae* and CAD. (5-10) These studies involve the examination of sera from CAD patients to determine the presence of elevated antibody levels (primarily immunoglobulins (Ig) G and IgA antibodies) to the organism. Following an acute infection, IgG antibody titers rise and then usually decrease slowly, whereas IgA antibodies tend to disappear more rapidly. The characteristics of antibody titers in patients with chronic infection are less well known; however, the persistence of elevated titers is generally considered to be a marker of a chronic infectious process. (7) Thus, these seroepidemiologic studies have examined elevated antibody titers as diagnostic criteria for chronic *C. pneumoniae* infection.

Saikku et al. provided the first serologic evidence of a relationship between bacteria and CAD in a small observational study in 1988. (6) These investigators examined serum samples from 40 male patients with acute myocardial infarction (MI), 30 male patients with chronic CAD and 41 control subjects. A total of sixty-eight percent of patients with acute MI and 50 % of patients with chronic CAD had elevated IgG and/or IgA antibody titers against *C. pneumoniae* as compared to 17% of control subjects ($p = 0.003$ for both acute MI and CAD groups versus control). Following this study, the same group of investigators examined 103 serum samples collected prospectively from patients involved in the Helsinki Heart Study. (7) These serum samples were collected three to six months before a cardiac endpoint (myocardial infarction or sudden cardiac death) and were matched with those from controls. Among case subjects with elevated IgA titers, the odds ratio (OR) for the development of CAD was 2.7 (95% confidence interval [CI] 1.1-6.5, $p = 0.02$). This relationship was found to be independent of other confounding factors such as age and smoking.

Mendall et al. demonstrated that 22 % of men with angiographically proven CAD ($n = 100$) had elevated titers of IgG antibody to *C. pneumoniae* as compared with 4.7% of age-matched controls. (8) The IgG titre associated with disease was independent of all other assessed risk factors at titers above 1:64. In another larger cross-sectional study of 388 men, a significant association between raised IgG titers to *C. pneumoniae* and CAD was demonstrated (OR 3.06; 95% CI 1.33-7.01), after adjustment for potential confounding factors. (5) Thom et al. evaluated 171 men, 55 years of age or younger, and women, 65 years of age or younger, who had at least one coronary artery lesion and compared them to 120 control patients. (9) Their results indicated that the OR for CAD associated with the presence of anti-*C. pneumoniae* antibody was 2.6 (95% CI 1.4-4.8).

Melnick et al. evaluated the sera from a subgroup of patients with asymptomatic carotid wall thickening involved in the Atherosclerosis Risk in Communities (ARIC) study and found that among the 326 case-control pairs, 73% of atherosclerotic cases had serologic

evidence of *C. pneumoniae* infection versus 63% of controls (OR 1.76, 95% CI 1.21-2.57). (10) After adjusting for confounding risk factors, the OR was 2.00 (95% CI 1.19-3.35). Further studies have subsequently identified similar associations between this organism and disease, adding to the growing body of seroepidemiological evidence. (1)

Histopathology

Examination of plaques from coronary and other arteries has provided more direct evidence of the possible involvement of *C. pneumoniae* in atherosclerotic disease. (11) In 1992 Shor et al. first detected *C. pneumoniae* in fatty streaks and atheromatous lesions in seven autopsy cases. (12) There are now over seventeen reports describing the detection of *C. pneumoniae* in cardiovascular lesions. (4) The presence of *C. pneumoniae* has been demonstrated in the atherosclerotic plaque using a variety of techniques, such as polymerase chain reaction (PCR), electron microscopy, immunostaining, and culture of the organism. (4) A wide range of detection rates exists between different investigators and with various techniques. Gibbs et al. conducted a summation analysis of data from fifteen papers that examined the prevalence of *C. pneumoniae* in atherosclerotic arterial lesions (n=597). (4) Eleven of these papers involved a comparison with non-atherosclerotic controls (n=131). The analysis demonstrated that 303 (50.8%) of the atherosclerotic arterial specimens were positive for *C. pneumoniae* against five (3.8%) of controls. Other authors have quoted similar figures in summarizing the histopathologic data. (2) The results indicate a greater prevalence of *C. pneumoniae* in atherosclerotic specimens; however, possible publication bias (i.e. non-publication of negative studies) may affect the rate of detection in this summation analysis. Finally, the presence of *C. pneumoniae* in atherosclerotic lesions is not proof that it has a role in the atherosclerotic process.

Mechanism

Despite evidence of its presence in patients with CAD and in atherosclerotic lesions, the actual role of *C. pneumoniae* in atherosclerosis remains unknown. There is no direct evidence that these organisms can cause the lesions of atherosclerosis. (13) However, several mechanisms by which *C. pneumoniae* may contribute to atherosclerosis have been proposed. Generally, infectious agents are thought to promote atherogenesis through both direct and indirect effects on vascular wall cells. (3) It is postulated that the presence of *C. pneumoniae* or its antigens within cells of the arterial wall acts as a stimulus to chronic inflammation. (4) *C. pneumoniae* commonly infects monocytes and chlamydial species can infect epithelial cells persistently under certain conditions. (14) The cytokine response from endothelial and smooth muscle cells, as well as from leukocytes, is regarded as an important mechanism in atherosclerosis-associated inflammation. (4) *C. pneumoniae* in human monocytes has been shown to induce production of cytokines, including tissue necrosis factor (TNF), interleukin (IL) 1-beta and IL-6, as part of the cell-mediated immune response. (4) In circulation, these cytokines promote a hypercoagulable state by activating platelets, increasing hepatic synthesis of acute-phase proteins (including fibrinogen) and inducing tissue factor release from endothelium with subsequent activation of the coagulation cascade. (4) TNF also inhibits the action of lipoprotein lipase leading to altered lipid metabolism, accumulation of serum triglycerides and a decrease in serum high density lipoprotein cholesterol (HDL-C), all of which produce a favourable environment for atherogenesis. (15) Seropositivity to *C. pneumoniae* has also been associated with elevated C-reactive protein (CRP), a marker of inflammation that is produced in response to IL-1 and IL-6. (16)

Antibiotic Therapy

The established association between *C. pneumoniae* infection and CAD determined by seroepidemiological and histopathological studies has led to the hypothesis that this organism causes or contributes to inflammation in atherosclerosis. This, in turn, has resulted in the completion of several clinical trials involving the use of antichlamydial antibiotics in patients with coronary artery atherosclerosis. (14,17-19)

The first of these studies was a prospective, randomized, double-blind, placebo-controlled trial involving 220 male patients. (17) In this trial, Gupta et al examined the effect of azithromycin, a macrolide antibiotic known to have good activity against *C. pneumoniae*, in a subgroup of post-MI patients. Antibodies to *C. pneumoniae* ("anti-Cp antibodies") were measured at baseline and at three months. Those patients with persisting seropositivity at greater than or equal to a 1:64 dilution on both occasions were randomized to receive either azithromycin 500 mg daily for three days for one course (n = 28), the same azithromycin regimen for two courses at a three month interval (n = 12), or placebo (n = 20). Patients without anti-Cp seropositivity on both occasions were not randomized to a treatment group. Adverse cardiovascular events (nonfatal MI, unstable angina, coronary angioplasty, urgent coronary artery bypass surgery or cardiovascular death) were monitored for 18 months from the original Cp titre determination. Both the nonrandomized and the randomized patients were followed. Those patients who received azithromycin demonstrated a five-fold reduction in cardiovascular events (OR 0.2 95% CI 0.05-0.8, p = 0.03) as compared with the combined group of non-randomized seropositive patients and those seropositive patients who received placebo only. The investigators rationalized the combination of data for the placebo and non-randomized seropositive patients based on the observation that there was no significant difference in cardiovascular risk factors or events between these two groups. Further justification for this data manipulation is not provided nor is there a clear definition of what type of patients comprised the non-randomized seropositive group. It appears that the non-randomized seropositive patients were those patients that had antibody titres greater than or equal to a 1:64 dilution at baseline but *not* at three months (and therefore not eligible for randomization) but again this is not clear. There was no difference between the treatment groups receiving either one or two courses of azithromycin with respect to cardiovascular event rate or proportion of patients with a decrease in anti-Cp titer.

Gurfinkel et al. conducted a randomized, double-blind trial involving 202 patients with unstable angina or non-Q-wave MI (Randomised Trial of Roxithromycin in non-Q wave Coronary Syndromes [ROXIS trial]). (18,19) Patients were randomly assigned to receive either roxithromycin 150 mg orally twice daily or placebo twice daily for thirty days. Randomization was independent of *C. pneumoniae* serostatus and patients were followed for six months. The primary end-point was a composite of three clinical outcomes including cardiac death, acute MI, and severe recurrent ischemia. The incidence of the composite endpoint was 9% in placebo recipients as compared to 2% in roxithromycin recipients (p = 0.032) at 30 days (end of treatment period). (18) The difference between composite endpoint rates were not statistically significant during the follow-up period at day 90 (12.5% versus 4.37%, placebo versus roxithromycin recipients, respectively, p = 0.065) and at day 180 (14.6% versus 8.69%, p = 0.259). (19) Baseline *C. pneumoniae* serology was performed and IgG antibodies were present at a titer of 1:64 or more in 47% of roxithromycin recipients and 49% of placebo recipients. No subset analysis on the effect of roxithromycin in seropositive versus seronegative subjects was performed. *C. pneumoniae* IgG titers, measured at baseline and at day 31, were unchanged in both groups. (19) The authors refer to this study as a 'pilot' as it was not adequately powered to find significance for the primary endpoint. This coupled with the lack of correlation with IgG titres make it difficult to draw conclusions from this study. Although not statistically significant, the difference in composite endpoint rates at thirty days for the roxithromycin group were postulated by the authors to be due either to an antichlamydial activity or anti-inflammatory activity.

The third published trial to examine the effects of antibiotics in CAD is the Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with Chlamydia (ACADEMIC) study. (14) In this study, 302 CAD patients with positive *C. pneumoniae* IgG titers ($\geq 1:16$) were randomized to receive either azithromycin 500 mg daily orally for three days followed by 500 mg per week for three months ($n = 150$) or placebo ($n = 152$). Global inflammatory marker scores (a composite of the circulating inflammatory markers CRP, IL-1, IL-6, and TNF- α), *C. pneumoniae* antibody titers, and cardiovascular events were assessed at three months and again at six months. At baseline, treatment groups were found to be similar, with an average age of 64 years and similar distribution of atherosclerotic risk factors. No difference in global inflammatory marker scores at the end of the three-month treatment period was observed. However, at six months the global inflammatory marker scores were lower in the azithromycin group, both for change scores ($p = 0.03$) and for actual value scores ($p = 0.01$). Antibody titers were found to be unaffected by therapy and the incidence of clinical cardiovascular events at six months did not differ between treatment groups (9 vs. 7 events for active drug and placebo groups, respectively). The authors reasoned that although the study was powered to assess the laboratory end points, for the clinical end point the event rate at six months was too low to demonstrate a clear therapeutic benefit. The investigators recognized that the event rate would be too low at six months and, therefore, the primary clinical endpoint was extended to two years. These results are not yet available.

The effect of various antibiotics on MI event rate has also been retrospectively assessed by Meier et al. using a general practice database in the United Kingdom. (20) A sample of 3,315 patients with a diagnosis of first time acute MI were compared with 13,139 controls without MI. Each patients' medical history for the previous three years was retrospectively examined. These investigators determined that the MI cases were less likely than the control cases to have used a tetracycline or a quinolone antibiotic in the past. In contrast, there was no association between MI occurrence and past use of macrolides, sulfonamides, penicillins or cephalosporins. The apparent lack of reduced risk with macrolides appears surprising; however, the author attributes this to the principal macrolide in use in this study sample, erythromycin (75% of total macrolide utilization), which is stated to be less efficacious against *C. pneumoniae*. These results appear to support the hypothesis that certain chronic bacterial infections may play a role in the etiology of ischemic heart disease but further conclusions cannot be drawn.

Summary

Seroepidemiological studies have confirmed an association between *C. pneumoniae* and atherosclerosis. Furthermore, histopathological studies have provided evidence for the presence of this microorganism in the atherosclerotic lesion. Although the association between *C. pneumoniae* and atherosclerosis has been established, the significance of this association and whether or not the organism contributes to the progression and complications of the disease are still unknown. Studies evaluating the effect of antibiotic treatment on cardiovascular events can be utilized to shed light on the potential etiologic role of *C. pneumoniae*. The three prospective antibiotic trials conducted to date provide inconclusive evidence. There are now at least two larger secondary prevention antibiotic trials underway namely the WIZARD (Weekly Intervention with Zithromax against Atherosclerotic-Related Disorders) and ACES (Azithromycin Coronary Events Study) trials that may be adequately powered to determine an effect on cardiac events. (21) If *C. pneumoniae* plays a role in the etiology of atherosclerosis and its complications, these secondary prevention studies should provide useful data to help us further elucidate this relationship. However, even with this evidence several issues will remain unanswered. The choice of optimal antibiotic regimens, duration of therapy, the relevance of the potential for non-antimicrobial effects of antibiotics and the role of other anti-chlamydial antibiotics will require further investigation. As well, the potential for widespread antibiotic resistance if chronic use of broad-spectrum drugs in this setting becomes

common will need consideration.

Acknowledgement

I would like to acknowledge Mario Bedard, Denis Belanger and Dina MacLeod, Department of Pharmacy, The Ottawa Hospital, Ottawa, Ontario, Canada for their invaluable contributions and editing during the preparation of this article.

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Is Coronary Artery Disease an Infectious Disease?

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Established risk factors for coronary artery disease (CAD) such as elevated serum lipids, smoking, hypertension, diabetes, age, gender, and family history are estimated to account for less than half the prevalence and severity of CAD. In searching for additional risk factors, the potential role of infection in the pathogenesis of atherosclerosis has received increasing attention. Based on the evidence from seroepidemiological studies, *Chlamydia pneumoniae* has emerged as the organism with the strongest apparent relationship with CAD. The first serological evidence emerged in 1988. Since then, several more studies have established the prevalence of this organism in patients with CAD. Histopathological studies have provided more direct evidence of *C. pneumoniae* in atherosclerotic lesions. However, despite evidence of its presence in patients with CAD, the significance of this association and whether or not the organism contributes to the progression and complications of the disease are unknown. Although several mechanisms by which *C. pneumoniae* may contribute to atherosclerosis have been postulated, the hypothesis that this organism contributes to inflammation in atherosclerosis has resulted in clinical trials of antichlamydial antibiotics in CAD patients. The results of the three trials completed to date have been inconclusive. Further evidence is required to establish the role of antibiotics in CAD. Currently, large secondary prevention trials are under way (WIZARD and ACES) which should help to elucidate whether *C. pneumoniae* plays a role in the etiology of atherosclerosis and its complications.

J Inform Pharmacother 2000;2:320-325.

Atherosclerosis, the pathological basis for coronary heart disease, is highly prevalent in Western

society and a major cause of mortality. (1) Established risk factors for coronary artery disease (CAD) such as elevated serum lipids, smoking, hypertension, diabetes, age, gender, and family history are estimated to account for less than half the prevalence and severity of CAD. (2) Many of the attributable risks for this disease remain unknown. In the search for additional risk factors, the potential role of infection in the pathogenesis of atherosclerosis has received recent attention. (1-13)

Several organisms have been studied to determine a potential relationship with CAD. The organisms most often implicated include herpes viruses (particularly cytomegalovirus), *Helicobacter pylori* and *Chlamydia pneumoniae*. (3) Based on seroepidemiologic and histopathologic evidence, *Chlamydia pneumoniae*, has emerged as the pathogen that appears to have the strongest apparent relationship. *C. pneumoniae* is a gram-negative obligatory intracellular bacteria responsible for a wide range of chronic, progressive, inflammatory conditions and is widely recognized as an important cause of respiratory tract infections. (4) This article will provide a brief overview of the evidence for *C. pneumoniae* in CAD and the preliminary evidence for the role of antibiotics in CAD.

Seroepidemiology

Many seroepidemiological studies have been completed over the past decade that provide evidence for an association between *C. pneumoniae* and CAD. (5-10) These studies involve the examination of sera from CAD patients to determine the presence of elevated antibody levels (primarily immunoglobulins (Ig) G and IgA antibodies) to the organism. Following

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an acute infection, IgG antibody titers rise and then usually decrease slowly, whereas IgA antibodies tend to disappear more rapidly. The characteristics of antibody titers in patients with chronic infection are less well known; however, the persistence of elevated titers is generally considered to be a marker of a chronic infectious process. (7) Thus, these seroepidemiologic studies have examined elevated antibody titers as diagnostic criteria for chronic *C. pneumoniae* infection.

Saikku et al. provided the first serologic evidence of a relationship between bacteria and CAD in a small observational study in 1988. (6) These investigators examined serum samples from 40 male patients with acute myocardial infarction (MI), 30 male patients with chronic CAD and 41 control subjects. A total of sixty-eight percent of patients with acute MI and 50 % of patients with chronic CAD had elevated IgG and/or IgA antibody titers against *C. pneumoniae* as compared to 17% of control subjects ($p = 0.003$ for both acute MI and CAD groups versus control). Following this study, the same group of investigators examined 103 serum samples collected prospectively from patients involved in the Helsinki Heart Study. (7) These serum samples were collected three to six months before a cardiac endpoint (myocardial infarction or sudden cardiac death) and were matched with those from controls. Among case subjects with elevated IgA titers, the odds ratio (OR) for the development of CAD was 2.7 (95% confidence interval [CI] 1.1-6.5, $p = 0.02$). This relationship was found to be independent of other confounding factors such as age and smoking.

Mendall et al. demonstrated that 22 % of men with angiographically proven CAD ($n = 100$) had elevated titers of IgG antibody to *C. pneumoniae* as compared with 4.7% of age-matched controls. (8) The IgG titre associated with disease was independent of all other assessed risk factors at titers above 1:64. In another larger cross-sectional study of 388 men, a significant association between raised IgG titers to *C. pneumoniae* and CAD was demonstrated (OR 3.06; 95% CI 1.33-7.01), after adjustment for potential confounding factors. (5) Thom et al. evaluated 171 men, 55 years of age or younger, and women, 65 years of age or younger, who had at least one coronary artery lesion and compared them to 120 control patients. (9) Their results indicated that the OR for

CAD associated with the presence of anti-*C. pneumoniae* antibody was 2.6 (95% CI 1.4-4.8).

Melnick et al. evaluated the sera from a subgroup of patients with asymptomatic carotid wall thickening involved in the Atherosclerosis Risk in Communities (ARIC) study and found that among the 326 case-control pairs, 73% of atherosclerotic cases had serologic evidence of *C. pneumoniae* infection versus 63% of controls (OR 1.76, 95% CI 1.21-2.57). (10) After adjusting for confounding risk factors, the OR was 2.00 (95% CI 1.19-3.35). Further studies have subsequently identified similar associations between this organism and disease, adding to the growing body of seroepidemiological evidence. (1)

Histopathology

Examination of plaques from coronary and other arteries has provided more direct evidence of the possible involvement of *C. pneumoniae* in atherosclerotic disease. (11) In 1992 Shor et al. first detected *C. pneumoniae* in fatty streaks and atheromatous lesions in seven autopsy cases. (12) There are now over seventeen reports describing the detection of *C. pneumoniae* in cardiovascular lesions. (4) The presence of *C. pneumoniae* has been demonstrated in the atherosclerotic plaque using a variety of techniques, such as polymerase chain reaction (PCR), electron microscopy, immunostaining, and culture of the organism. (4) A wide range of detection rates exists between different investigators and with various techniques. Gibbs et al. conducted a summation analysis of data from fifteen papers that examined the prevalence of *C. pneumoniae* in atherosclerotic arterial lesions ($n=597$). (4) Eleven of these papers involved a comparison with non-atherosclerotic controls ($n=131$). The analysis demonstrated that 303 (50.8%) of the atherosclerotic arterial specimens were positive for *C. pneumoniae* against five (3.8%) of controls. Other authors have quoted similar figures in summarizing the histopathologic data. (2) The results indicate a greater prevalence of *C. pneumoniae* in atherosclerotic specimens; however, possible publication bias (i.e. non-publication of negative studies) may affect the rate of detection in this summation analysis. Finally, the presence of *C. pneumoniae* in atherosclerotic

lesions is not proof that it has a role in the atherosclerotic process.

Mechanism

Despite evidence of its presence in patients with CAD and in atherosclerotic lesions, the actual role of *C. pneumoniae* in atherosclerosis remains unknown. There is no direct evidence that these organisms can cause the lesions of atherosclerosis. (13) However, several mechanisms by which *C. pneumoniae* may contribute to atherosclerosis have been proposed. Generally, infectious agents are thought to promote atherogenesis through both direct and indirect effects on vascular wall cells. (3) It is postulated that the presence of *C. pneumoniae* or its antigens within cells of the arterial wall acts as a stimulus to chronic inflammation. (4) *C. pneumoniae* commonly infects monocytes and chlamydial species can infect epithelial cells persistently under certain conditions. (14) The cytokine response from endothelial and smooth muscle cells, as well as from leukocytes, is regarded as an important mechanism in atherosclerosis-associated inflammation. (4) *C. pneumoniae* in human monocytes has been shown to induce production of cytokines, including tissue necrosis factor (TNF), interleukin (IL) 1-beta and IL-6, as part of the cell-mediated immune response. (4) In circulation, these cytokines promote a hypercoagulable state by activating platelets, increasing hepatic synthesis of acute-phase proteins (including fibrinogen) and inducing tissue factor release from endothelium with subsequent activation of the coagulation cascade. (4) TNF also inhibits the action of lipoprotein lipase leading to altered lipid metabolism, accumulation of serum triglycerides and a decrease in serum high density lipoprotein cholesterol (HDL-C), all of which produce a favourable environment for atherogenesis. (15) Seropositivity to *C. pneumoniae* has also been associated with elevated C-reactive protein (CRP), a marker of inflammation that is produced in response to IL-1 and IL-6. (16)

Antibiotic Therapy

The established association between *C. pneumoniae* infection and CAD determined by seroepidemiological and histopathological studies has

led to the hypothesis that this organism causes or contributes to inflammation in atherosclerosis. This, in turn, has resulted in the completion of several clinical trials involving the use of antichlamydial antibiotics in patients with coronary artery atherosclerosis. (14,17-19)

The first of these studies was a prospective, randomized, double-blind, placebo-controlled trial involving 220 male patients. (17) In this trial, Gupta et al examined the effect of azithromycin, a macrolide antibiotic known to have good activity against *C. pneumoniae*, in a subgroup of post-MI patients. Antibodies to *C. pneumonia* ("anti-Cp antibodies") were measured at baseline and at three months. Those patients with persisting seropositivity at greater than or equal to a 1:64 dilution on both occasions were randomized to receive either azithromycin 500 mg daily for three days for one course (n = 28), the same azithromycin regimen for two courses at a three month interval (n = 12), or placebo (n = 20). Patients without anti-Cp seropositivity on both occasions were not randomized to a treatment group. Adverse cardiovascular events (nonfatal MI, unstable angina, coronary angioplasty, urgent coronary artery bypass surgery or cardiovascular death) were monitored for 18 months from the original Cp titre determination. Both the nonrandomized and the randomized patients were followed. Those patients who received azithromycin demonstrated a five-fold reduction in cardiovascular events (OR 0.2 95% CI 0.05-0.8, p = 0.03) as compared with the combined group of non-randomized seropositive patients and those seropositive patients who received placebo only. The investigators rationalized the combination of data for the placebo and non-randomized seropositive patients based on the observation that there was no significant difference in cardiovascular risk factors or events between these two groups. Further justification for this data manipulation is not provided nor is there a clear definition of what type of patients comprised the non-randomized seropositive group. It appears that the non-randomized seropositive patients were those patients that had antibody titres greater than or equal to a 1:64 dilution at baseline but *not* at three months (and therefore not eligible for randomization) but again this is not clear. There was no difference between the treatment groups receiving either one or two courses of azithromycin with respect to

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cardiovascular event rate or proportion of patients with a decrease in anti-Cp titer.

Gurfinkel et al. conducted a randomized, double-blind trial involving 202 patients with unstable angina or non-Q-wave MI (Randomised Trial of Roxithromycin in non-Q wave Coronary Syndromes [ROXIS trial]). (18,19) Patients were randomly assigned to receive either roxithromycin 150 mg orally twice daily or placebo twice daily for thirty days. Randomization was independent of *C. pneumoniae* serostatus and patients were followed for six months. The primary end-point was a composite of three clinical outcomes including cardiac death, acute MI, and severe recurrent ischemia. The incidence of the composite endpoint was 9% in placebo recipients as compared to 2% in roxithromycin recipients ($p = 0.032$) at 30 days (end of treatment period). (18) The difference between composite endpoint rates were not statistically significant during the follow-up period at day 90 (12.5% versus 4.37%, placebo versus roxithromycin recipients, respectively, $p = 0.065$) and at day 180 (14.6% versus 8.69%, $p = 0.259$). (19) Baseline *C. pneumoniae* serology was performed and IgG antibodies were present at a titer of 1:64 or more in 47% of roxithromycin recipients and 49% of placebo recipients. No subset analysis on the effect of roxithromycin in seropositive versus seronegative subjects was performed. *C. pneumoniae* IgG titers, measured at baseline and at day 31, were unchanged in both groups. (19) The authors refer to this study as a 'pilot' as it was not adequately powered to find significance for the primary endpoint. This coupled with the lack of correlation with IgG titres make it difficult to draw conclusions from this study. Although not statistically significant, the difference in composite endpoint rates at thirty days for the roxithromycin group were postulated by the authors to be due either to an antichlamydial activity or anti-inflammatory activity.

The third published trial to examine the effects of antibiotics in CAD is the Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with Chlamydia (ACADEMIC) study. (14) In this study, 302 CAD patients with positive *C. pneumoniae* IgG titers ($\geq 1:16$) were randomized to receive either azithromycin 500 mg daily orally for three days followed by 500 mg per week for three months ($n = 150$) or placebo ($n = 152$). Global inflammatory

marker scores (a composite of the circulating inflammatory markers CRP, IL-1, IL-6, and TNF- α), *C. pneumoniae* antibody titers, and cardiovascular events were assessed at three months and again at six months. At baseline, treatment groups were found to be similar, with an average age of 64 years and similar distribution of atherosclerotic risk factors. No difference in global inflammatory marker scores at the end of the three-month treatment period was observed. However, at six months the global inflammatory marker scores were lower in the azithromycin group, both for change scores ($p = 0.03$) and for actual value scores ($p = 0.01$). Antibody titers were found to be unaffected by therapy and the incidence of clinical cardiovascular events at six months did not differ between treatment groups (9 vs. 7 events for active drug and placebo groups, respectively). The authors reasoned that although the study was powered to assess the laboratory end points, for the clinical end point the event rate at six months was too low to demonstrate a clear therapeutic benefit. The investigators recognized that the event rate would be too low at six months and, therefore, the primary clinical endpoint was extended to two years. These results are not yet available.

The effect of various antibiotics on MI event rate has also been retrospectively assessed by Meier et al. using a general practice database in the United Kingdom. (20) A sample of 3,315 patients with a diagnosis of first time acute MI were compared with 13,139 controls without MI. Each patients' medical history for the previous three years was retrospectively examined. These investigators determined that the MI cases were less likely than the control cases to have used a tetracycline or a quinolone antibiotic in the past. In contrast, there was no association between MI occurrence and past use of macrolides, sulfonamides, penicillins or cephalosporins. The apparent lack of reduced risk with macrolides appears surprising; however, the author attributes this to the principal macrolide in use in this study sample, erythromycin (75% of total macrolide utilization), which is stated to be less efficacious against *C. pneumoniae*. These results appear to support the hypothesis that certain chronic bacterial infections may play a role in the etiology of ischemic heart disease but further conclusions cannot be drawn.

Summary

Seroepidemiological studies have confirmed an association between *C. pneumoniae* and atherosclerosis. Furthermore, histopathological studies have provided evidence for the presence of this microorganism in the atherosclerotic lesion. Although the association between *C. pneumoniae* and atherosclerosis has been established, the significance of this association and whether or not the organism contributes to the progression and complications of the disease are still unknown. Studies evaluating the effect of antibiotic treatment on cardiovascular events can be utilized to shed light on the potential etiologic role of *C. pneumoniae*. The three prospective antibiotic trials conducted to date provide inconclusive evidence. There are now at least two larger secondary prevention antibiotic trials underway namely the WIZARD (Weekly Intervention with Zithromax against Atherosclerotic-Related Disorders) and ACES (Azithromycin Coronary Events Study) trials that may be adequately powered to determine an effect on cardiac events. (21) If *C. pneumoniae* plays a role in the etiology of atherosclerosis and its complications, these secondary prevention studies should provide useful data to help us further elucidate this relationship. However, even with this evidence several issues will remain unanswered. The choice of optimal antibiotic regimens, duration of therapy, the relevance of the potential for non-antimicrobial effects of antibiotics and the role of other anti-chlamydial antibiotics will require further investigation. As well, the potential for widespread antibiotic resistance if chronic use of broad-spectrum drugs in this setting becomes common will need consideration.

Acknowledgement

I would like to acknowledge Mario Bedard, Denis Belanger and Dina MacLeod, Department of Pharmacy, The Ottawa Hospital, Ottawa, Ontario, Canada for their invaluable contributions and editing during the preparation of this article.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2000;2:400.

Suitability of Warfarin Self-Management in a Random Population

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University of British Columbia Pharmacy 405 (Directed Studies) Research Presentation Seminar (Podium presentation). Vancouver, British Columbia, Canada. April 7, 2000. (Unfunded study).

Context

Patient self-management of oral anticoagulation using a home INR monitor has been shown to provide superior anticoagulation control compared to traditional physician-managed therapy. Patients in these studies are carefully selected, therefore there is little information about the applicability of this strategy to the general population.

Objectives

To determine the feasibility of anticoagulation self-management in a group of cardiac patients in a cardiothoracic surgery step-down unit.

Setting

A cardiothoracic surgery step-down patient unit in a 1000-bed Canadian tertiary teaching hospital.

Design

This was a two-phase study conducted over a four-month period. *Phase I:* Consecutive inpatients prescribed warfarin were randomly assessed on post-operative day 4-5 for eligibility of self-management. Using a questionnaire format, patients were evaluated for fluency in English, medication compliance, interest in self-management, willingness to document INR results and warfarin doses administered, manual dexterity and comfort with finger pricking. *Phase II:* All patients were contacted at home 4 weeks after the initial in hospital contact to confirm eligibility for self-management.

Main Outcome Measures

The primary outcome measure was the proportion of patients suitable for warfarin self-management at post-operative day 4-5 and at home 4 weeks later. Secondary outcome measures were patient characteristics that appear to influence patient suitability.

Results

Forty-two patients were evaluated during the period November 1999 to March 2000. The majority of patients (81%) were receiving warfarin for a mechanical heart valve. Twenty-six patients (62%) were deemed suitable for self-management during Phase I, while 25 (60%) were considered suitable during Phase II. Of the 17 patients who were deemed ineligible at final contact, the reasons included a preference for physician-management (9), reluctance with finger pricking (3) or documentation of results (1), lack of english comprehension (2) and mental incompetence (2). Preliminary evaluation suggests that older age (68 yrs vs. 58 yrs), female gender and prior warfarin use negatively effect patient suitability.

Conclusions

Based upon the preliminary results of this study, it appears that a substantial proportion of cardiac patients are potential candidates for self-management of their anticoagulation.

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Pharmacotherapy on the Web

The Journal of Informed Pharmacotherapy 2000;2:500.

TheHeart.org, National Guidelines Clearinghouse, Dictionary of Pharmaceutical Medicine, DISCERN Online, Free Medical Journals.com, Therapeutics Initiative, MedErrors.com

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Name of site:	TheHeart.org: Cardiology Online
Type of site:	Cardiology database
Authoring organization:	Eric Topol, MD
Sponsors:	Conceptis Technologies Inc & corporate sponsors (banner ads indicate pharmaceutical industry is a source of revenue).
Of particular interest to:	Cardiologists, interventionalists & clinicians caring for people with disorders of the heart and circulation, and on preventing such disorders.
Completeness Score (/5)	4
Credibility Score (/5)	4.5
Usability Score (/5)	5
Why is it useful? (what will it help me DO?):	Allows clinicians to keep up-to-date with daily updates on all aspects of cardiology (newly published trials, conference proceedings, new drug launches etc.)
Commentary:	1. A user-friendly, searchable database to discover what others are thinking regarding recently published trials. 2. Timely debates, insights, commentaries and reviews on controversial trial results from renowned clinicians. 3. Good multi-media education features on topics of current interest. 4. The Forum is useful for viewing, posting or responding to questions (although the possibility for misinformation exists). All disease states should have a website designed as well as this one!
URL of site:	http://www.theheart.org
Reviewed by:	Anne Nguyen, Pharm.D.

Name of site:	National Guidelines Clearinghouse
Type of site:	Clinical practice guidelines databank
Authoring organization:	Agency for Healthcare Research and Quality, American Medical Association, American Association of Health Plans
Sponsors:	As above.
Of particular interest to:	Any clinical practitioner or health policymaker
Completeness Score (/5)	3.5
Credibility Score (/5)	4
Usability Score (/5)	4
Why is it useful? (what will it help me DO?):	This site allows users to locate and view clinical guidelines more rapidly than by traditional methods such as literature searching.
Commentary:	The National Guideline Clearinghouse is a specialized index of the medical literature pertaining only to clinical practice guidelines. Most of the guidelines on the site have been published in mainstream peer-reviewed journals and have been excerpted by the NGC staff. Fortunately, most of the guidelines are available in their original full-text form (or even PDF form) with graphics and diagrams as well. Guidelines can be browsed in a number of ways, but the most powerful feature is the SEARCH engine which locates keywords and topics across all the guidelines on the site. The database is extensive. One limitation is that there is a significant delay between publication and indexing by NGC, so users should beware of missing guidelines published within the last year or so and use old-fashioned MEDLINE or PUBMED searching for recent guidelines. Also, I was unable to find a couple of guidelines I know were published in major journals more than a year ago, so it would appear that this site is not completely authoritative in its guideline listings. Finally, the pitfalls of reliance on guidelines, mainly due to their typical lack of adherence to evidence-based principles (<u>Lancet</u>, Jan. 8, 2000) have been well documented.
URL of site:	http://www.guideline.gov
Reviewed by:	Peter Loewen, Pharm.D.

Name of site:	Dictionary of Pharmaceutical Medicine
Type of site:	Online dictionary of pharmaceutical acronyms and abbreviations.
Authoring organization:	Christian Nordqvist (Webmaster), Pharma-Lexicon International, United Kingdom
Sponsors:	As above.
Of particular interest to:	Any healthcare worker who needs a handy online reference source for this type of information.
Completeness Score (/5)	4.5

Credibility Score (/5)	4
Usability Score (/5)	4.5
Why is it useful? (what will it help me DO?)	This is a repository of unique information that is not easily found elsewhere. Where else can you find out what the acronym "NASS" stands for?
Commentary:	In addition to functioning as an online acronym/abbreviation reference (the database currently contains 16,000 acronyms), this site also has a good selection of links to sites regarding clinical trials, generic names, companies, hospitals (world and US), wholesalers, colleges, associations, directories, regulatory data, jobs, country profiles, news, health ministries, and journals. The site also has a discussion group and appears to be updated regularly. Check it out.
URL of site:	http://www.pharma-lexicon.com/
Reviewed by:	Peter Jewesson, Ph.D.

Name of site:	DISCERN Online
Type of site:	Evaluation tool for consumer health information
Authoring organization:	Deborah Charnock, Sasha Shepperd
Sponsors:	NHS Executive Research & Development Programme
Of particular interest to:	Patients, Health care providers who make decisions about treatments.
Completeness Score (/5)	5
Credibility Score (/5)	4
Usability Score (/5)	4
Why is it useful? (what will it help me DO?)	It is a unique tool to help consumers and clinicians evaluate the quality of information they are presented with.
Commentary:	In light of the recent NEJM article (June 1, 2000) which demonstrated that the major media by which consumers learn about treatments generally provide incomplete descriptions of the risks and benefits of therapy, this online tool seems particularly timely. The final numerical score produced is only partly helpful in enabling consumers and clinicians to decide whether or not to use a treatment. Its usefulness stems mainly from its ability to challenge readers of health information to ask specific questions and gives hints about what constitutes "good" information versus "bad" information and then to quantify their analysis.
URL of site:	http://www.discern.org.uk
Reviewed by:	Peter Loewen, Pharm.D.

Name of site:	Free Medical Journals.com

Type of site:	Index of online medical journals
Authoring organization:	Bernd Sebastian Kamps, M.D., Ph.D.
Sponsors:	Flying Publisher
Of particular interest to:	All clinical practitioners and researchers.
Completeness Score (/5)	4.5
Credibility Score (/5)	5
Usability Score (/5)	4
Why is it useful? (what will it help me DO?):	It enables rapid access to medical journals which provide free full-text online.
Commentary:	Have you ever found an article citation and wondered whether you can get it free online rather than go to the library to photocopy it, or worse, to pay a document delivery service charge? Well, this site is the most up-to-date index of journals which provide free full-text access to their contents online. Several sites attempt to provide such indexes, but none are updated as frequently, index non-English language journals, or log journals which have recently discontinued free online access (e.g. JAMA) as thoroughly as this one. Before you go to the library to photocopy something, check this site to see whether your target journal is listed. Of course, this site is only a directory of journals. What you actually find at the journal's site will vary widely.
URL of site:	http://www.freemedicaljournals.com
Reviewed by:	Peter Loewen, Pharm.D.

Name of site:	Therapeutics Initiative
Type of site:	Evidence-based drug therapy information
Authoring organization:	Therapeutics Initiative
Sponsors:	University of British Columbia
Of particular interest to:	Pharmacotherapy practitioners in all disciplines
Completeness Score (/5)	4
Credibility Score (/5)	4
Usability Score (/5)	3
Why is it useful? (what will it help me DO?):	It provides well-written evidence-based reviews of individual drugs or therapy for specific disease states.

Commentary: This site's primary feature is the "Therapeutics Letter" which is available in full-text online. The "Letter" provides concise, evidence-based reviews of specific drugs or diseases which are topical, up-to-date and written by practitioners. The target audience for the Letter is general practitioners and pharmacists. The TI prides itself on it's lack of affiliation with the pharmaceutical industry and this generally translates into a high degree of objectivity about new drugs in the Therapeutics Letter.

The design of the site is not pretty (lots of blinking animated gif's and wallpaper), but links to the information of interest are large and easy to find.

URL of site: <http://www.ti.ubc.ca>

Reviewed by: [Peter Loewen](#), Pharm.D.

Name of site: [MedErrors.com](#)

Type of site: Specialized site cataloging medication error information

Authoring organization: Bridge Medical, Inc.

Sponsors: Bridge Medical, Inc.

Of particular interest to: Pharmacists and hospital administrators

Completeness Score 3
(/5)

Credibility Score (/5) 3

Usability Score (/5) 4

Why is it useful? (what will it help me DO?): Provides a forum for discussion about medication errors within health systems.

Commentary: The sponsor of this site is a consulting company which specializes in helping hospitals reduce medication errors. As such, the credibility of some of the information must be scrutinized. Fortunately, most of the information is directly verifiable from the peer-reviewed literature. Users may find the "Digest" section is particularly useful as it documents experiences of health care providers and the problems and solutions they have encountered in reducing medication errors. The "Library" section is also potentially useful as a database of published literature on medication errors. Overall, this highly specialized site is unique and may be useful for someone trying to characterize and tackle medication error issues within their organization.

URL of site: <http://www.mederrors.com>

Reviewed by: [Peter Loewen](#), Pharm.D.

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Journal of Informed Pharmacotherapy 2000;3 (October-December)

Editorial

- Updated "Canadian Guidelines" for Community-Acquired Pneumonia: Use With Caution
Peter J. Jewesson



Evidence-Based Reviews of the Pharmacotherapeutic Literature

with emphasis on interpretation of the findings, designed to help practitioners put the findings into proper perspective

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Updated
April 15, 2002

Editorial

Updated "Canadian Guidelines" for Community-Acquired Pneumonia: Use with Caution

Consider a disease that accounts for hundreds of thousands of hospital admissions and tens of thousands of deaths per year. A disease that, despite our best efforts, still boasts a mortality rate of at least one in every ten patients afflicted. Community-acquired pneumonia (CAP) is just that disease and it is the leading cause of death by infection.

In this issue, Dr. Alfred Gin provides us with a succinct review of the issues and controversies surrounding the management of CAP. (1) As Gin describes, CAP has been the subject of considerable attention over the past decade. Despite this interest, many issues persist. *Streptococcus pneumoniae* remains the most common pathogen causing CAP; however, treatment has become more complex as the susceptibility patterns for this organism are changing. The incidence of *S. pneumoniae* with some degree of resistance to penicillin has increased three-fold in the US over a 7-year period and about five-fold in Canada over the last decade. While true in vitro resistance appears to be relatively uncommon (and possibly declining) in Canada, conditions in the U.S. are somewhat worse. Why our resistance patterns are different to those of our southern neighbours is still unknown. Perhaps it is related to the relative restrictions and use of antimicrobials. No doubt a number of factors are at work here. Controversy also exists regarding the most appropriate breakpoints to describe sensitivities for *S. pneumoniae*. Recommendations have apparently been made to increase the MIC breakpoints that we use to define resistance. Doing so will reduce the reported prevalence of penicillin resistance and we will again need to reconsider our treatment choices. Gin also reminds us that *S. pneumoniae* resistance to fluoroquinolones appears to be linked to first-generation agent utilization rates. A relationship we should keep in mind when considering the new guidelines.

Annual CAP-related costs in the US are estimated to be \$8 billion. If we apply the usual 10% rule to account for population size differences between the U.S. and Canada, that would suggest that the annual costs in our country are approximately \$800 million. Needless to say, the costs to society (and the potential profits for the pharmaceutical industry) associated with the treatment of CAP are substantial. It is no wonder that this disease has captured the attention of the pharmaceutical manufacturers and that there are so many agents available in the marketplace to treat this affliction.

Most importantly, Gin alerts us to the recent publication of the Canadian Guidelines for the Initial Management of CAP. (2) After a 7-year hiatus, these guidelines have been updated and, for the first time, are now available on line. While not explicitly stated, these guidelines are directed at the initial management of CAP in adult patients only. Little emphasis is placed upon the continued treatment and monitoring of patients who either respond to or fail on initial therapy. In addition, no information regarding pneumonia in pediatric patients is provided.

The guidelines were created by a group who denote themselves the Canadian Community-Acquired

Pneumonia Working Group, although some of the members are actually from the U.S. and abroad. To accomplish this task, select members of the Canadian Infectious Diseases Society (CIDS), the Canadian Thoracic Society (CTS) and additional members from the U.S. apparently separated into 3 teams who were individually responsible for addressing epidemiology, risk factors and etiology, and treatment. According to the authors, the teams met for two days in early 1999, formulated drafts, circulated these to the members, sought an external review by colleagues in the US, Europe and Israel and then finalized the guidelines based upon the input received. With the possible exception of one individual with dual Pharm.D./Ph.D. degrees, there was no apparent involvement or collaboration with individuals or groups outside of the medical discipline. Now that's consensus building. Perhaps the members support the position of the Infectious Diseases Society of America (as written by the selective membership of the Clinical Affairs Committee and the Antimicrobial Use and Clinical Trials Committees) who promote a limited role of pharmacists in the management of infections? (3) I truly hope this is not the case, as no one discipline would be fully functional without the collaboration of the balance. The guidelines would have been stronger if their creation had been a true interdisciplinary effort as well as international exercise. Certainly, we owe it to our patients to work synergistically on their behalf.

That said, I must applaud the authors of the guidelines for what must have constituted a significant amount of coordination and work. When properly done, practice guidelines can be a useful tool to help us translate research evidence into clinical decision aids (4). The creation of this particular comprehensive, well-referenced guidelines document aimed at influencing the management of CAP in Canada required an extensive and detailed systematic review of the literature. The authors state that they were required to review 585 published papers or abstracts for the treatment section alone. Whether this was accomplished with or without external sponsorship is unknown. Unfortunately, no information was provided by the journal or the authors regarding the source (or absence) of external funding for this worthwhile exercise.

Let's add some further context to these guidelines. Although they have been denoted "Canadian guidelines", it would be more accurate to simply describe these as "2000 CIDS/CTS Guidelines" for the management of community-acquired pneumonia, much as the Infectious Diseases Society of America has done with the publication of their recent practice guidelines. (5) It would be an oversimplification to assume that these guidelines can be applied uniformly across this vast country with its inherent regional and local differences in bacterial susceptibility patterns, patient characteristics, access to health care and other factors. While the authors describe these new guidelines as "...an evidence-based update", they responsibly also state that "...it is important to recognize that these recommendations are derived by the consensus of experts and not entirely based on evidence from randomized clinical trials". I will try to illustrate this critical qualifying statement with an example.

One of the more significant changes to the list of empirical choices for the initial management of CAP is the addition of the so-called "*respiratory fluoroquinolones*". These agents are apparently denoted as such because they possess enhanced in vitro activity against the pathogens typically responsible for CAP, in particular *S. pneumoniae*. I personally believe that the term "*respiratory fluoroquinolone*" was conceived as a marketing ploy aimed at associating this group of drugs with a particular type of infection. What a useful "handle" to promote a particular drug in the increasingly confusing milieu of fluoroquinolones. What other antimicrobial do you know that has been linked to a particular anatomical structure and its related infections? Do we denote cefuroxime a "respiratory cephalosporin" or erythromycin as a "respiratory macrolide"? Of the list of respiratory fluoroquinolones identified by the authors of the guidelines, grepafloxacin has been withdrawn from the market due to cardiac toxicity

and trovafloxacin is restricted to use in the hospital setting due to reports of severe liver toxicity. Not a sterling track record for the new fluoroquinolones. Neither gatifloxacin nor moxifloxacin are as yet available in Canada. Although available, ofloxacin is mysteriously missing from the text (perhaps the authors incorrectly took to heart the suggested synonyms supplied by MS Word when spell checking this word). That's a shame. Unfortunately, that leaves us with only one agent, levofloxacin.

According to the new guidelines, levofloxacin has now been elevated to the role of drug of first choice for the treatment of CAP in patients with chronic obstructive lung disease who have received antibiotics or corticosteroids within the past 3 months; nursing home residents or hospitalized patients in the non-intensive care unit setting; and as second line therapy in patients with suspected macroaspiration (in combination with clindamycin or metronidazole). Let's briefly examine the evidence behind this selection.

While the authors describe that there are at least 16 published clinical trials involving comparisons of monotherapy with various respiratory fluoroquinolones against other fluoroquinolones, macrolides and cephalosporins, seven of these are in abstract form only. Until these undergo appropriate peer-review, these publications should be considered research findings only and should be used with great caution when considering the management of a particular patient, let alone the creation of national guidelines. According to the guidelines authors, only three clinical trials have been published in which levofloxacin has been directly compared to standard therapy for CAP. (6,7,8) Two of these studies have undergone peer-review and have been published in reputable journals. (6,7) The third report is a conference abstract for which there appears to be no follow-up full report. (8) Again, while the study is large, the information has not been subjected to appropriate peer-review.

The two published peer-reviewed studies involved industry-sponsored open-label or unblinded study designs in which levofloxacin was compared to a variety of cephalosporin regimens. The study by File et al. involved 590 patients of which 456 (226 parenteral and/or oral levofloxacin 500mg once daily, 230 ceftriaxone 1g or 2g Q12-24H and/or cefuroxime axetil 500mg Q12H) were considered by the authors to be evaluable for clinical efficacy. (6) The decision to use an intravenous or oral antimicrobial agent for initial therapy was made by the investigator. Erythromycin or doxycycline could be added to the comparator arm at the investigator's discretion. Remember, this is an unblinded trial. No intention-to-treat analysis was apparently conducted. Clinical success at 5-7 days post therapy was reported to be superior for the levofloxacin group (96%) as compared to the ceftriaxone and/or cefuroxime axetil group (90%) (95% confidence interval [CI] of -10.7 to -1.3). Whether anyone would consider a 1% difference in clinical outcomes to be superior is debatable, particularly in light of the variability in regimens employed and the unblinded nature of this company-sponsored trial. In this particular study, there was a relatively low incidence of *S. pneumoniae* and *Haemophilus influenzae* (isolated in 15 and 12% of clinically evaluable patients, respectively) and a relatively high incidence of atypical organisms. These are conditions that would favour antimicrobials (or combinations if employed) with activity against the latter pathogens. The second unblinded study by Norrby et al. involved 625 patients who were enrolled and randomized to receive parenteral and/or oral levofloxacin (500mg Q12H) or ceftriaxone (4 g/d). (7) Of these, 6 patients received no treatment and the remaining 619 (levofloxacin 314, ceftriaxone 305) patients constituted what the authors describe as their intention-to-treat group. At the end of treatment there were only 266 patients (127 levofloxacin, 139 ceftriaxone) who had completed the study protocol. At the clinical endpoint (2-5 d after the end of treatment), the cure rates for levofloxacin and ceftriaxone were similar in both the intention to treat analysis (76% and 75%, respectively) and completed protocol analysis (87% and 86%, respectively).

To summarize, we have two industry-sponsored, unblinded and methodologically dissimilar clinical trials involving about 1,200 enrolled patients in which variable regimens of parenteral or oral levofloxacin were compared to variable regimens of two cephalosporins (at the discretion of the investigators). Levofloxacin appears to be superior to its comparators in one trial and equivalent to the comparator in the other. Consider this evidence when you apply the guidelines to the many thousands of patients we will treat for CAP every year. Once again, the qualifying statement by the authors of the guidelines ring true. This particular recommendation (and some others in the document) was based upon consensus opinion and was made in the absence of an abundance of solid evidence. Combine this with the fact that, like any other drug class, the increased use of respiratory fluoroquinolones can be expected to lead to an increased incidence of bacterial resistance and we have an interesting conundrum. As pointed out by Gin, preliminary reports of respiratory fluoroquinolone resistance-related treatment failures have already surfaced this year. Time will only tell how long the clinical utility half-life of the newer fluoroquinolones will be. As aptly recommended by Hooper (9), in order to preserve the therapeutic opportunities that the most recent generation of fluoroquinolones provide, our challenge will be to ensure that we use these drugs wisely. Most community-acquired respiratory infections are still caused by pathogens that remain susceptible to beta-lactam drugs and macrolides. Fluoroquinolones should only be used in clinical situations where they offer a clear therapeutic advantage over other drug classes.

There are many other issues to consider when treating CAP, but I'll close with one only. As described by Cook et al (4), not all the outcomes of interest are measured in all primary studies. Certain measures, such as quality of life, are often inadequately represented in reviews. This can be no better illustrated than in the context of CAP management. While we should continue to strive to eradicate the organism, clear the x-ray and reduce the fever...what definitive evidence do we have that we have actually improved the patient's quality of life, let alone reduced mortality?

In summary, while the newly published guidelines certainly provide us with a very useful summary of our present understanding of the epidemiology, risk factors, etiology, diagnosis and treatment of CAP, they do not represent new knowledge. What is the take home message? Apply these guidelines where appropriate, but not without an understanding of their limitations. As Cook also describes, "...no matter how they are developed and implemented, guidelines may do more harm than good if they are inappropriately interpreted or applied". (4)

Peter J. Jewesson, PhD FCSHP
Publishing Co-Editor

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J Inform Pharmacother 2000;3:1.

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Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2000;3:200-202.

Amiodarone to Prevent Recurrence of Atrial Fibrillation: Its all a matter of rhythm

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Reviewer's profession/specialty: Pharmacy/Internal Medicine

Original Citation

Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M et al. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. *N Engl J Med* 2000;342:913-20.
[PubMed Cit](#)

Overall Study Question

To determine whether amiodarone is superior to sotalol or propafenone in converting and maintaining normal sinus rhythm in patients with a recent history of symptomatic atrial fibrillation (AF). Patients: Subjects who had an electrocardiographically confirmed episode of symptomatic atrial fibrillation (lasting 10 minutes or longer) within the preceding six months for which long-term antiarrhythmic drug therapy was planned. Outcome variables: primary end point was length of time to a first electrocardiographically confirmed recurrence of symptomatic atrial fibrillation (lasting 10 minutes or more). Intervention: Amiodarone was compared to the aggregate of Sotalol and Propafenone (patients randomized in 2:1:1 ratio for A:S:P) Amiodarone: 10 mg per kilogram of body weight each day for 14 days, followed by 300 mg per day for 4 weeks, then daily maintenance dose of 200 mg. Sotalol: 80-160 mg bid, depending on age, sex and renal function. Propafenone: 150mg q8h - 300mg q12h, depending on weight and age. All patients who did not convert to NSR within several days of starting drug therapy were electrically cardioverted. All patients were anticoagulated.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Patients were randomized to amiodarone or to either sotalol or propafenone (2:1:1 randomization).

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. All patients were accounted for and an intention-to-treat analysis was used. The investigators reported that 2.5% of patients were lost to follow-up. Eleven sotalol and 13 propafenone patients received another antiarrhythmic drug during the trial period.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

No. This study was open-label. Primary events were subjective (eg. symptoms of AF) and only resulted in an ECG evaluation if spontaneously reported by the subjects. Thus, clinician/patient biases about the drugs may have influenced the likelihood of reporting of symptoms. Treatment assignment was unaffected by the patients' presentation, and therefore was unaffected by the open-label design.

4. Were the groups similar at the start of the trial?

Yes. Except for the fact that more patients in the sotalol/propafenone groups had left ventricular hypertrophy (LVH) (21% vs. 13%). No adjustment was reported for this factor in the main results. However, a subgroup analysis presented in the paper shows that patients with LVH were associated with a higher risk of AF recurrence (i.e. treatment failure). Thus, it has been hypothesized that if the incidence of LVH was the same in both groups, the difference in efficacy between amiodarone and sotalol/propafenone would have been smaller.

5. Aside from the experimental intervention, were the groups treated equally?

Yes. Except for the fact that amiodarone patients received more chest X-rays and thyroid function tests than other patients for the purpose of monitoring for adverse effects.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

Over the 468-day follow-up period, 35% of amiodarone and 63% of sotalol or propafenone-

treated patients experienced recurrence of atrial fibrillation (NNT with amiodarone vs. sotalol/propafenone for 1.3 years to achieve one additional recurrence-free patient = 4 ($p < 0.001$)). Because a minority of patients in the amiodarone group experienced the primary endpoint, the median time to recurrence could not be calculated. For the sotalol/propafenone groups, the median time to recurrence was 98 days. There was no difference between sotalol and propafenone. There were no differences in overall mortality or arrhythmic death. Thirty-four percent of amiodarone and 46% of sotalol/propafenone patients discontinued due to adverse effects (NNH for one additional drug discontinuation over 1.3 years = 9 ($p < 0.01$)).

2. How precise was the estimate of the treatment effect?

The hazard ratio for recurrence of atrial fibrillation in the amiodarone group was 0.43 (95% CI 0.32 - 0.57). These confidence intervals are fairly narrow and even at their upper bound, represent a clinical effect which is likely to be clinically significant.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. These results represent the first compelling data of the superiority efficacy of amiodarone versus commonly used antiarrhythmics for chronic prevention of AF. The study also demonstrated that low-dose amiodarone is better tolerated than the other drugs and does not cause serious adverse effects over the length of this study.

2. Were all clinically important outcomes considered?

Yes.

3. Are the likely treatment benefits worth the potential harms and costs?

Yes. Serious toxicities (e.g. pulmonary fibrosis, thyroid dysfunction, ventricular arrhythmias, oculotoxicity) were rare and not more common than observed in the sotalol/propafenone groups.

Commentary

This Medical Research Council of Canada-funded and well-designed study provides convincing support for the preferential use of amiodarone in patients with AF for the chronic suppression of symptoms. However, the open label design may have resulted in an expectation bias on the part of investigators and/or patients who expected amiodarone to be more effective for whatever reason. This may have resulted in an overestimation of the benefits of amiodarone. There was a high degree of initial conversion to NSR in all three groups during the first 3 weeks of therapy, but this was not maintained as well in the sotalol/propafenone groups. Only 12% of patients had left ventricular dysfunction and the

applicability of these results to such patients is questionable, despite the commonly-encountered clinical scenario of AF in the presence of congestive heart failure. Despite this, amiodarone is likely the safest of the three drugs studied in patients with left ventricular dysfunction. Longer-term and larger trials are required to determine whether the benefits seen in this trial confer other morbidity (e.g. stroke, cardiovascular events) and/or mortality benefits.

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Amiodarone to Prevent Recurrence of Atrial Fibrillation: Its all a matter of rhythm

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Original Citation

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1. Was assignment of patients randomized?

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2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. All patients were accounted for and an intention-to-treat analysis was used. The investigators reported that 2.5% of patients were lost to follow-up. Eleven sotalol and 13 propafenone patients received another antiarrhythmic drug during the trial period.

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4. Were the groups similar at the start of the trial?

Yes. Except for the fact that more patients in the sotalol/propafenone groups had left ventricular hypertrophy (LVH) (21% vs. 13%). No adjustment was reported for this factor in the main results. However, a subgroup analysis presented in the paper shows that patients with LVH were associated with a higher risk of AF recurrence (i.e. treatment failure). Thus, it has been hypothesized that if the incidence of LVH was the same in both groups, the difference in efficacy between amiodarone and sotalol/propafenone would have been smaller.

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J Inform Pharmacother 2000;3:200-202.

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2000;203-205.

Celecoxib vs. nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: A touch of CLASS?

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Original Citation

Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A et al. Gastrointestinal toxicity with celecoxib vs. nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA* 2000;284:1247-55. [PubMed Cit](#)

Overall Study Question

The primary objective of this trial was to compare the annualized incidence of upper GI ulcer complications (gastric or duodenal perforation, gastric outlet obstruction or upper GI bleeding) in osteoarthritis (OA) or rheumatoid arthritis (RA) adult patients treated with celecoxib (at dosages 2-4-fold higher than recommended by the FDA) or an NSAID (diclofenac or ibuprofen).

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Patients were randomly assigned to receive celecoxib 400mg twice daily; ibuprofen 800 mg 3 times daily; or diclofenac 75 mg twice daily.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. Of the 8,059 patients randomized, 3,987 received celecoxib and 3,981 received NSAID treatment (1,985 ibuprofen and 1,996 received diclofenac). Approximately equal numbers (44 and 47 respectively) of patients did not receive treatment as assigned. When compared to the celecoxib arm, more patients withdrew in the NSAID treatment arms as a result of adverse events (20.6% vs. 18.4%, $p=0.01$) or lack of therapeutic effect (14.8% vs. 12.6%, $p=0.005$). No patients were lost to follow up. Analysis of the primary outcome was by intention to treat such that all patients who had received at least one dose of the assigned study medication were included.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. All treatment regimens were double-blinded and double-dummy. Unblinding occurred in three instances, although none were related to a study outcome.

4. Were the groups similar at the start of the trial?

Yes. Baseline characteristics between the celecoxib and NSAID groups (combined) did not differ significantly. All measured potential confounding variables were equally balanced across groups.

5. Aside from the experimental intervention, were the groups treated equally?

Yes. All patients were treated equally from both diagnostic and therapeutic perspectives. Outcomes were adjudicated by a blinded GI events committee not involved in the care of the patient.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

The annualized incidence of upper GI ulcer complications was 0.76% in the celecoxib group as compared to 1.45% in the NSAID groups ($p=0.09$). This translates into an ARR of 0.69% and a NNT of 145 patients (CI 60 to -1098) treated for one year to avoid one upper GI ulcer complication.

Secondary analyses revealed that the annualized incidence of upper GI ulcer complications plus symptomatic ulcers was 2.08% in the celecoxib arm as compared to 3.54% in the NSAID arms (ARR 1.46%, NNT 69 patients treated for one year to avoid one

event, $p=0.02$). In patients on concurrent low dose ASA, the potential reduction in GI toxicity of celecoxib as compared to the NSAID was not evident. However, in non-ASA users, the annualized incidence of upper GI ulcer complications was significantly lower with celecoxib as compared to the NSAID groups (ARR 0.83%, NNT to avoid one upper GI ulcer complication for one year was 121, $p=0.04$).

2. How precise was the estimate of the treatment effect?

For the primary outcome (upper GI ulcer complications) the 95% CI for the RR crossed one indicating the possibility of a null result and thus, an imprecise estimate of the effect. The 95% CI for the RR for the secondary outcome variables were fairly wide, but none crossed one.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. This study is the first to show that there likely is a reduction in clinically important GI events in patients treated with COX-2 specific inhibitors. However, at best, this effect is modest and may be nullified by the presence of low dose ASA.

2. Were all clinically important outcomes considered?

Yes. The outcomes considered were clinically important.

3. Are the likely treatment benefits worth the potential harms and costs?

This question is really what needs to be addressed with further research. It is unclear if the modest reduction in GI events with celecoxib translates into a reduction in overall treatment costs that will compensate for the higher acquisition cost of the drug.

Commentary

It would appear that the incidence of upper GI ulcer complications plus symptomatic ulcer is lower in patients treated with celecoxib than those on regular non-specific COX inhibitors. In addition, it would appear that the annualized incidence of upper GI complications is reduced through the use of celecoxib in patients not receiving low dose ASA. However, both of these outcomes were secondary in the CLASS trial. The primary outcome, the annualized incidence of upper GI complications in all study entrants, was not significantly different between the study arms although there was a trend for a modest reduction in events in the celecoxib arm. Since the use of concomitant anti-ulcer drugs was prohibited, it is unclear how the differences would manifest in real world use of these agents. In addition, the cost-effectiveness of celecoxib as compared to traditional non-specific COX inhibitors has not been established. Considering the widespread use of these agents, further research is warranted to determine both their economic impact and the outcomes achieved when used outside of a clinical trial.

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1. Marra CA, Esdaile JM, Sun H, Anis AH. The cost of COX inhibitors: How selective should we be? J Rheumatol 2000 (in press).

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Celecoxib vs. nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: A touch of CLASS?

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Reviewer's profession/specialty: Pharmacy/Research/Rheumatology; funded by CIHR/Arthritis Society Fellowship Award, Vancouver, B.C., Canada.

Original Citation

Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A et al. Gastrointestinal toxicity with celecoxib vs. nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA* 2000;284:1247-55.

Overall Study Question

The primary objective of this trial was to compare the annualized incidence of upper GI ulcer complications (gastric or duodenal perforation, gastric outlet obstruction or upper GI bleeding) in osteoarthritis (OA) or rheumatoid arthritis (RA) adult patients treated with celecoxib (at dosages 2-4-fold higher than recommended by the FDA) or an NSAID (diclofenac or ibuprofen).

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. Patients were randomly assigned to receive celecoxib 400mg twice daily; ibuprofen 800 mg 3 times daily; or diclofenac 75 mg twice daily.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. Of the 8,059 patients randomized, 3,987 received celecoxib and 3,981 received NSAID treatment (1,985 ibuprofen and 1,996 received diclofenac). Approximately equal numbers (44 and 47 respectively) of patients did not receive treatment as assigned. When compared to the celecoxib arm, more patients withdrew in the NSAID treatment arms as a result of adverse events (20.6% vs. 18.4%, $p=0.01$) or lack of therapeutic effect (14.8% vs. 12.6%, $p=0.005$). No patients were lost to follow up. Analysis of the primary outcome was by intention to treat such that all patients who had received at least one dose of the assigned study medication were included.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. All treatment regimens were double-blinded and double-dummy. Unblinding occurred in three instances, although none were related to a study outcome.

4. Were the groups similar at the start of the trial?

Yes. Baseline characteristics between the celecoxib and NSAID groups (combined) did not differ

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significantly. All measured potential confounding variables were equally balanced across groups.

5. Aside from the experimental intervention, were the groups treated equally?

Yes. All patients were treated equally from both diagnostic and therapeutic perspectives. Outcomes were adjudicated by a blinded GI events committee not involved in the care of the patient.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

The annualized incidence of upper GI ulcer complications was 0.76% in the celecoxib group as compared to 1.45% in the NSAID groups ($p=0.09$). This translates into an ARR of 0.69% and a NNT of 145 patients (CI 60 to -1098) treated for one year to avoid one upper GI ulcer complication.

Secondary analyses revealed that the annualized incidence of upper GI ulcer complications plus symptomatic ulcers was 2.08% in the celecoxib arm as compared to 3.54% in the NSAID arms (ARR 1.46%, NNT 69 patients treated for one year to avoid one event, $p=0.02$). In patients on concurrent low dose ASA, the potential reduction in GI toxicity of celecoxib as compared to the NSAID was not evident. However, in non-ASA users, the annualized incidence of upper GI ulcer complications was significantly lower with celecoxib as compared to the NSAID groups (ARR 0.83%, NNT to avoid one upper GI ulcer complication for one year was 121, $p=0.04$).

2. How precise was the estimate of the treatment effect?

For the primary outcome (upper GI ulcer complications) the 95% CI for the RR crossed one indicating the possibility of a null result and thus, an imprecise estimate of the effect. The 95% CI for the RR for the secondary outcome variables were fairly wide, but none crossed one.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. This study is the first to show that there likely is a reduction in clinically important GI events in patients treated with COX-2 specific inhibitors. However, at best, this effect is modest and may nullified by the presence of low dose ASA.

2. Were all clinically important outcomes considered?

Yes.

3. Are the likely treatment benefits worth the potential harms and costs?

This question is really what needs to be addressed with further research. It is unclear if the modest reduction in GI events with celecoxib translates into a reduction in overall treatment costs that will compensate for the higher acquisition cost of the drug.

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Commentary

It would appear that the incidence of upper GI ulcer complications plus symptomatic ulcer is lower in patients treated with celecoxib than those on regular non-specific COX inhibitors. In addition, it would appear that the annualized incidence of upper GI complications is reduced through the use of celecoxib in patients not receiving low dose ASA. However, both of these outcomes were secondary in the CLASS trial. The primary outcome, the annualized incidence of upper GI complications in all study entrants, was not significantly different between the study arms although there was a trend for a modest reduction in events in the celecoxib arm. Since the use of concomitant anti-ulcer drugs was prohibited, it is unclear how the differences would manifest in real world use of these agents. In addition, the cost-effectiveness of celecoxib as compared to traditional non-specific COX inhibitors has not been established. Considering the widespread use of these agents, further research is warranted to determine both their economic impact and the outcomes achieved when used outside of a clinical trial.

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1. Marra CA, Esdaile JM, Sun H, Anis AH. The cost of COX inhibitors: How selective should we be? *J Rheumatol* 2000 (in press).

J Inform Pharmacother 2000;3:203-205.

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2000;3:206-208.

Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: Another viable option?

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Reviewer's profession/specialty: Ambulatory Care, Neurology

Original Citation

Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis. *JAMA* 1999;282:1344-52. [PubMed Cit](#)

Overall Study Question

This randomized, double-blind, placebo-controlled, parallel-group study was conducted at 110 study centres across North America. It was designed to test the efficacy of risedronate 2.5mg and 5mg compared to placebo given daily over 3 years in reducing the incidence of vertebral and other fractures in women who were at least 5 years post menopause, no older than 85 years of age, and had either 2 or more radiographically identified vertebral fractures or had one vertebral fracture with bone mineral density measurements that were at least 2 standard deviations below the mean for young adults. The main outcome measure was the incidence of patients with new vertebral fractures. Secondary outcome measures included the cumulative incidence of non-vertebral fractures, change in bone mineral density (BMD) and markers of bone turnover, and overall incidence of adverse events. All subjects received calcium 1000mg/day taken with the evening meal. For subjects with baseline levels of 25-hydroxyvitamin D less than 40nmol/L, supplementation with Vitamin D (cholecalciferol) up to 500IU/day was provided.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. All patients were randomly and equally assigned into one of three groups and received either risedronate 2.5mg, risedronate 5mg or placebo. Patients across all three groups had similar demographics reported.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. All patients who were randomized in the study were properly accounted for. However, due to a protocol amendment after the first year, the risedronate 2.5mg arm of the study was terminated. The investigators report on the disposition of the subjects in the 2.5mg group until withdrawal due to the protocol amendment. Overall, 9,400 patients were screened and 2,258 met the study criteria. These individuals were randomized to receive risedronate 2.5mg (n = 811), risedronate 5mg (n = 813) or placebo (n = 815). Nineteen patients were not treated. Ten of these patients voluntarily withdrew from the study while 9 were involved in protocol violations. Four hundred and eighty-nine risedronate 5mg and 450 placebo recipients completed the 3-year study.

3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. All patients and investigators were blind to the treatment including the radiologists who performed the vertebral fracture assessments. As the incidence of adverse events reported was similar, this would suggest that unblinding due to adverse effects would not be an issue.

4. Were the groups similar at the start of the trial?

Yes. All baseline demographics were similar between the three treatment arms at the start of the trial.

5. Aside from the experimental intervention, were the groups treated equally?

Yes. All subjects received calcium 1000mg/day taken with the evening meal. Subjects with baseline levels of 25-hydroxyvitamin D less than 40nmol/L received supplementation with Vitamin D (cholecalciferol) up to 500IU/day. The specific dose of Vitamin D administered was not specified.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

The proportion of subjects with at least 1 incident vertebral fracture over the 3 year study period (primary endpoint) was 11.3% for the risedronate 5mg group and 16.3% for the placebo group (relative risk 0.59 [95%CI 0.43-82]), $p=0.003$). This represents an absolute risk reduction of 5% or a number needed to treat of 20 over three years. The cumulative incidence of non-vertebral fractures (secondary outcome) over 3 years of treatment was 5.2% for risedronate 5mg and 8.4% for placebo (relative risk 0.6 [95%CI 0.39-0.94, $p=0.02$] which corresponds to an absolute risk reduction of 3.2% or a NNT of 32 over three years.

Over 3 years, the subjects in the 5mg risedronate group had significant increases in BMD compared to placebo for the following areas measured: lumbar spine (5.4%), femoral neck (1.6%), and femoral trochanter (3.3%). Markers of bone turnover (i.e. bone-specific alkaline phosphatase and the deoxypyridinoline-creatinine ratio) were available for only 32% of study subjects and, in comparison with placebo, declined with risedronate treatment. The overall incidence of adverse effects was similar between the risedronate 5mg (34%) and placebo (29%) groups. Serious adverse events were observed in 29% and 27% of the groups, respectively. Since bisphosphonates are known to commonly cause upper gastrointestinal tract adverse effects, the investigators also reported the incidence of any upper gastrointestinal adverse events (30% vs. 27% for risedronate 5mg and placebo groups). The groups also appeared to have a similar incidence of specific gastrointestinal symptoms.

2. How precise was the estimate of the treatment effect?

The relative risk 95% CI for the cumulative incidence of vertebral fractures over the 3 years revealed a statistically significant effect. In my opinion, the effect is clinically relevant and the reduction of incident vertebral fractures is clinically important.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

Yes. The information in this study further supports the premise that risedronate can effectively reduce the incidence of vertebral fractures and that this drug may also reduce non-vertebral fractures in postmenopausal women who are at high risk for fractures, including those who have previously experienced fractures. The treatment was not associated with an increase in adverse events in the clinical trial setting.

2. Were all clinically important outcomes considered?

Yes. Although incident vertebral fractures were the primary endpoint, a more clinically relevant endpoint is hip fractures. The current study investigated non-vertebral fractures as a secondary endpoint and the authors found a statistical significance between groups. Subjects in the risedronate 5mg and placebo, experienced 14 vs. 22 wrist fractures, 12 vs. 15 hip and/or pelvis

fractures, 4 vs. 10 humerus fractures, 4 vs. 8 leg fractures and 3 vs. 0 clavicle fractures, respectively. An investigation of hip fractures as a primary endpoint is currently underway.

3. Are the likely treatment benefits worth the potential harms and costs?

This is difficult to determine. The cost of the drug is significantly higher than the cost of calcium and vitamin D and the reduction in vertebral fractures can mean different symptoms and effects for different people. Some vertebral fractures occur without the patients being aware, others cause pain, and after many vertebral fractures, deformity is apparent. However, there is emerging evidence that previous vertebral fractures are a major risk factor for more fractures, including hip and wrist fractures. It may be a cyclical phenomenon that increases exponentially with the accumulation of more fractures and it could be interpreted that by reducing the incidence of vertebral fractures may slow or prevent this cascade.

Commentary

This study involved a sufficient sample size to detect a difference in fracture rate associated with risedronate therapy for non-vertebral fractures that are clearly clinically relevant. Unfortunately, this type of fracture was only a secondary endpoint in this trial. Since this study was placebo-controlled and thus did not involve other alternatives currently used to reduce fractures in this population, it is difficult to determine the current role of this drug. This study does, however, demonstrate that risedronate appears to be an effective agent for the reduction of vertebral fractures in this population and that this drug may also reduce the incidence of non-vertebral fractures. Another advantage of this study is that subjects with previous or active gastrointestinal illnesses or concomitant use of ASA or an NSAID were included. These patient groups have been excluded in some of the earlier trials involving bisphosphonates. Finally, this study shows that risedronate is certainly another option available to help reduce vertebral fractures in this study population that can be generalized to our practice population.

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Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: Another viable option?

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Original Citation

Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis. *JAMA* 1999;282:1344-52.

Overall Study Question

This randomized, double-blind, placebo-controlled, parallel-group study was conducted at 110 study centres across North America. It was designed to test the efficacy of risedronate 2.5mg and 5mg compared to placebo given daily over 3 years in reducing the incidence of vertebral and other fractures in women who were at least 5 years post menopause, no older than 85 years of age, and had either 2 or more radiographically identified vertebral fractures or had one vertebral fracture with bone mineral density measurements that were at least 2 standard deviations below the mean for young adults. The main outcome measure was the incidence of patients with new vertebral fractures. Secondary outcome measures included the cumulative incidence of non-vertebral fractures, change in bone mineral density (BMD) and markers of bone turnover, and overall incidence of adverse events. All subjects received calcium 1000mg/day taken with the evening meal. For subjects with baseline levels of 25-hydroxyvitamin D less than 40nmol/L, supplementation with Vitamin D (cholecalciferol) up to 500IU/day was provided.

Are the Results of the Study Valid?

1. Was assignment of patients randomized?

Yes. All patients were randomly and equally assigned into one of three groups and received either risedronate 2.5mg, risedronate 5mg or placebo. Patients across all three groups had similar demographics reported.

2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?

Yes. All patients who were randomized in the study were properly accounted for. However, due to a protocol amendment after the first year, the risedronate 2.5mg arm of the study was terminated. The investigators report on the disposition of the subjects in the 2.5mg group until withdrawal due to the protocol amendment. Overall, 9,400 patients were screened and 2,258 met the study criteria. These individuals were randomized to receive risedronate 2.5mg (n = 811), risedronate 5mg (n = 813) or placebo (n = 815). Nineteen patients were not treated. Ten of these patients voluntarily withdrew from the study while 9 were involved in protocol violations. Four hundred and eighty-nine risedronate 5mg and 450 placebo recipients completed the 3-year study.

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3. Were patients, their clinicians, and study personnel 'blind' to treatment?

Yes. All patients and investigators were blind to the treatment including the radiologists who performed the vertebral fracture assessments. As the incidence of adverse events reported was similar, this would suggest that unblinding due to adverse effects would not be an issue.

4. Were the groups similar at the start of the trial?

Yes. All baseline demographics were similar between the three treatment arms at the start of the trial.

5. Aside from the experimental intervention, were the groups treated equally?

Yes. All subjects received calcium 1000mg/day taken with the evening meal. Subjects with baseline levels of 25-hydroxyvitamin D less than 40nmol/L received supplementation with Vitamin D (cholecalciferol) up to 500IU/day. The specific dose of Vitamin D administered was not specified.

6. Overall, are the results of the study valid?

Yes.

What were the Results?

1. How large was the treatment effect?

The proportion of subjects with at least 1 incident vertebral fracture over the 3 year study period (primary endpoint) was 11.3% for the risedronate 5mg

group and 16.3% for the placebo group (relative risk 0.59 [95%CI 0.43-82]), $p=0.003$). This represents an absolute risk reduction of 5% or a number needed to treat of 20 over three years. The cumulative incidence of non-vertebral fractures (secondary outcome) over 3 years of treatment was 5.2% for risedronate 5mg and 8.4% for placebo (relative risk 0.6 [95%CI 0.39-0.94, $p=0.02$] which corresponds to an absolute risk reduction of 3.2% or a NNT of 32 over three years.

Over 3 years, the subjects in the 5mg risedronate group had significant increases in BMD compared to placebo for the following areas measured: lumbar spine (5.4%), femoral neck (1.6%), and femoral trochanter (3.3%). Markers of bone turnover (i.e. bone-specific alkaline phosphatase and the deoxypyridinoline-creatinine ratio) were available for only 32% of study subjects and, in comparison with placebo, declined with risedronate treatment. The overall incidence of adverse effects was similar between the risedronate 5mg (34%) and placebo (29%) groups. Serious adverse events were observed in 29% and 27% of the groups, respectively. Since bisphosphonates are known to commonly cause upper gastrointestinal tract adverse effects, the investigators also reported the incidence of any upper gastrointestinal adverse events (30% vs. 27% for risedronate 5mg and placebo groups). The groups also appeared to have a similar incidence of specific gastrointestinal symptoms.

2. How precise was the estimate of the treatment effect?

The relative risk 95% CI for the cumulative incidence of vertebral fractures over the 3 years revealed a statistically significant effect. In my opinion, the effect is clinically relevant and the reduction of incident vertebral fractures is clinically important.

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Will the Results Help Me in Caring for My Patients? Commentary

1. Can the results be applied to my patient care?

Yes. The information in this study further supports the premise that risedronate can effectively reduce the incidence of vertebral fractures and that this drug may also reduce non-vertebral fractures in postmenopausal women who are at high risk for fractures, including those who have previously experienced fractures. The treatment was not associated with an increase in adverse events in the clinical trial setting.

2. Were all clinically important outcomes considered?

Yes.

3. Are the likely treatment benefits worth the potential harms and costs?

This is difficult to determine. The cost of the drug is significantly higher than the cost of calcium and vitamin D and the reduction in vertebral fractures can mean different symptoms and effects for different people. Some vertebral fractures occur without the patients being aware, others cause pain, and after many vertebral fractures, deformity is apparent. However, there is emerging evidence that previous vertebral fractures are a major risk factor for more fractures, including hip and wrist fractures. It may be a cyclical phenomenon that increases exponentially with the accumulation of more fractures and it could be interpreted that by reducing the incidence of vertebral fractures may slow or prevent this cascade.

This study involved a sufficient sample size to detect a difference in fracture rate associated with risedronate therapy for non-vertebral fractures that are clearly clinically relevant. Unfortunately, this type of fracture was only a secondary endpoint in this trial. Since this study was placebo-controlled and thus did not involve other alternatives currently used to reduce fractures in this population, it is difficult to determine the current role of this drug. This study does, however, demonstrate that risedronate appears to be an effective agent for the reduction of vertebral fractures in this population and that this drug may also reduce the incidence of non-vertebral fractures. Another advantage of this study is that subjects with previous or active gastrointestinal illnesses or concomitant use of ASA or an NSAID were included. These patient groups have been excluded in some of the earlier trials involving bisphosphonates. Finally, this study shows that risedronate is certainly another option available to help reduce vertebral fractures in this study population that can be generalized to our practice population.

J Inform Pharmacother 2000;3:206-208.

Evidence Based Review Article

The Journal of Informed Pharmacotherapy 2000;2:209-211.

Can garlic be used as a cholesterol-lowering agent? Perhaps its better used for warding off evil

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Original Citation

Stevinson C, Pittler MH, Ernst E. Garlic for treating hypercholesterolemia. A meta-analysis of randomized clinical trials. *Ann Intern Med* 2000;133:420-9. [PubMed Cit](#)

Overall Study Question

Two previous meta-analyses have been published on the effect of garlic on serum total cholesterol levels. The last meta-analysis was published in 1994 and several independent studies have conducted since this time. The objective of the current article was to conduct a an updated meta-analysis of all studies meeting the inclusion criteria and to thus reassess the effect of garlic (as compared to placebo) on total serum cholesterol in patients with elevated (i.e. greater than 5.17 mmol/L) levels. No efforts were made by the investigators to distinguish between studies that focused on patients with coronary heart disease (CHD) versus those without.

Are the Results of the Study Valid?

1. Did the overview address a focused clinical question?

Yes.

2. Were the criteria used to select articles for inclusion appropriate?

Yes. In order to be included in the meta-analysis, studies were required to be of

randomized, double-blind, and placebo-controlled design. Furthermore, treatments were required to include single entity garlic preparations, patients enrolled in the clinical trials had to have had elevated total cholesterol levels of at least 5.17 mmol/L, and total cholesterol levels had to be an endpoint of the included study. It is unclear as to whether or not studies were required to have used total cholesterol as the primary endpoint (vs. secondary) in order to be included in the meta-analysis.

3. Is it unlikely that important, relevant studies were missed?

Yes. The authors utilized a variety of databases from European and United States sources to identify relevant articles. Searches were performed from the earliest date each database was created through to November 1998. Efforts were made to identify additional published or unpublished articles by contacting experts in the field, manufacturers of garlic preparations, and by searching the bibliographies of all papers. Articles of all languages were reviewed. Thirty nine studies were identified, however, 13 met the inclusion criteria and thus were included in the analysis.

4. Was the validity of the included studies appraised?

Yes. The quality of the methods utilized by each study identified was assessed using a scale which quantified the likelihood of bias of the trial based upon the description of the randomization, blinding, and patient withdrawals. The article did not indicate the score (if any) that was needed to be attained in order for a study to be included in the analysis.

5. Were assessments of studies reproducible?

Yes. The meta-analysis used the chi-square test although the specific type of test used was not identified. This test for heterogeneity was significant indicating statistical heterogeneity amongst the trials. The heterogeneity was due to one study in particular. When study was excluded, homogeneity between the remaining 12 studies was found. No further tests for heterogeneity were undertaken.

What were the Results?

1. What are the overall results of the review?

Thirty-nine studies were identified, however only 13 met the inclusion criteria for meta-analysis. There were 796 patients enrolled in the 13 studies, 10 trials reported benefits with garlic, while 3 found no difference as compared to placebo. Overall, the meta-analysis revealed that garlic significantly ($p < 0.01$) reduced total cholesterol levels. Treatment with garlic resulted in a 5.8% reduction in total cholesterol levels from baseline. The authors did not report the reduction in cholesterol levels that occurred with placebo. The authors also evaluated the effect of garlic on total cholesterol levels using the 12 homogenous studies and found a smaller (4.3%) reduction in cholesterol levels with

garlic. Gastrointestinal symptoms and garlic breath were the most frequently reported adverse effects. It is unclear if there were significant differences in the incidence of adverse effects between the garlic and placebo groups.

2. How precise were the results?

Among the 13 studies included, treatment with garlic resulted in a 5.8% reduction in total cholesterol levels from baseline. The weighted mean difference was - 0.41 mmol/L (95% CI, -0.66 to -0.15 mmol/L). Among the 12 homogenous studies, the reduction in total cholesterol levels with garlic was 4.3%, equivalent to a mean difference of -0.30 mmol/L (95% CI, - 0.48 to - 0.11 mmol/L).

3. How much does allowance for uncertainty change the results?

Two sensitivity analyses were performed. The first analysis utilized 5 methodologically similar studies (i.e. same garlic preparation, same dose and also controlled for dietary factors). No significant difference in the reduction of total cholesterol with garlic (as compared to placebo) was found. The second analysis included 6 of diet-controlled studies and, once again, the authors found no significant difference between garlic and placebo in the reduction of cholesterol.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

No. While the current meta-analysis found garlic to reduce total cholesterol levels by at best 5.8%, there are numerous unanswered questions which make applying the results of this trial to direct patient care difficult. The reduction in cholesterol levels seen with garlic is considerably less than that seen with other effective lipid-lowering interventions, such as diet or the HMG-CoA reductase inhibitors. Furthermore, it is unclear from this analysis of the effect of garlic on other endpoints that are more relevant than total cholesterol levels such as the incidence of coronary heart disease, mortality, and morbidity. While this analysis included all patients with elevated total cholesterol levels, it is unclear whether specific groups of patients would derive greater benefit (i.e. those with or without CHD, elevated low-density lipoprotein, or low high-density lipoprotein. It is also unclear as to the length of therapy required with garlic to derive a 5.8% reduction. The duration of therapy of the studies included in the meta-analysis ranged from 8 weeks to 24 weeks. The benefits of longer therapy are unknown.

2. Were all clinically important outcomes considered?

No. While the use of total cholesterol as a study endpoint is easily measured, it is not the most relevant endpoint to evaluate. Future studies should focus on clinically relevant endpoints, such as the effects of garlic on the specific lipoproteins, such as the atherogenic low-density lipoprotein or high-density lipoprotein, or clinical outcomes, for example total mortality, the incidence of CHD, or death from myocardial infarction and/or CHD.

3. Are the benefits worth the harms and costs?

No. The benefit of garlic in reducing cholesterol levels, in the absence of other relevant clinical endpoints, is likely not worth the costs, despite the minimal adverse effects observed. Lipid-lowering diets are more cost effective than garlic. Furthermore, patients can derive greater cholesterol reductions with diet therapy alone.

Commentary

Cardiovascular disease, of which CHD is the most common, is the leading cause of death in Canada. Elevated cholesterol is an independent risk factor for heart disease. Numerous studies have shown that the incidence of coronary heart disease and elevated cholesterol to be continuous and graded. Numerous large, randomized, controlled trials have shown that reducing cholesterol levels with HMG-CoA reductase inhibitors, in patients with and without CHD, and with elevated and "average" cholesterol levels reduces mortality and morbidity. In addition to knowing which patients derive the greatest benefit from therapy, the duration of therapy required to obtain benefits, the side effects from these medications are known, and for the most part, minimal. In order to be considered an "alternative" to standard therapies, studies evaluating other forms of lipid-lowering interventions, such as garlic, need to evaluate clinically relevant endpoints, as have the HMG-CoA reductase trials. In the absence of these studies, recommending these "alternative" interventions is difficult. Numerous unanswered questions exist from the current meta-analysis on the use of garlic in reducing total cholesterol levels. As previously mentioned, there are no data on the effect of garlic on the incidence of coronary heart disease, reductions in fatal or non-fatal myocardial infarctions, hospital admissions, or total mortality. Furthermore, it is unclear which types of patients derive the greatest benefit. The meta-analysis included patients with and without CHD and children. The form of garlic administered to patients enrolled in the studies varied from essential oil to standardized powder, or spray-dried powder. Whether there are differences in endpoints based upon the form of garlic used is unknown. Furthermore, the dose of garlic required is unknown. Patients inquiring about the use of garlic for reducing cholesterol should be informed of the minimal reduction in cholesterol levels observed in clinical trials and the aforementioned pitfalls of the current literature. Future randomized, controlled studies of garlic, should evaluate specific groups of patients, specific garlic preparations and doses, and evaluate clinically important endpoints.

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Can garlic be used as a cholesterol-lowering agent? Perhaps its better used for warding off evil

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Reviewer's profession/specialty: Research Fellow, EPICORE Centre and Division of Cardiology, University of Alberta, Edmonton, Alberta, Canada.

Original Citation

Stevinson C, Pittler MH, Ernst E. Garlic for treating hypercholesterolemia. A meta-analysis of randomized clinical trials. *Ann Intern Med* 2000;133:420-9.

Overall Study Question

Two previous meta-analyses have been published on the effect of garlic on serum total cholesterol levels. The last meta-analysis was published in 1994 and several independent studies have conducted since this time. The objective of the current article was to conduct a an updated meta-analysis of all studies meeting the inclusion criteria and to thus reassess the effect of garlic (as compared to placebo) on total serum cholesterol in patients with elevated (i.e. greater than 5.17 mmol/L) levels. No efforts were made by the investigators to distinguish between studies that focused on patients with coronary heart disease (CHD) versus those without.

Are the Results of the Study Valid?

1. Did the overview address a focused clinical question?

Yes.

2. Were the criteria used to select articles for inclusion appropriate?

Yes. In order to be included in the meta-analysis, studies were required to be of randomized, double-blind, and placebo-controlled design. Furthermore, treatments were required to include single entity garlic preparations, patients enrolled in the clinical trials had to have had elevated total cholesterol levels of at least 5.17 mmol/L, and total cholesterol levels had to be an endpoint of the included study. It is unclear as to whether or not studies were required to have used total cholesterol as the primary endpoint (vs. secondary) in order to be included in the meta-analysis.

3. Is it unlikely that important, relevant studies were missed?

Yes. The authors utilized a variety of databases from European and United States sources to identify relevant articles. Searches were performed from the earliest date each database was created through to November 1998. Efforts were made to identify additional published or unpublished articles by contacting experts in the field, manufacturers of garlic preparations, and by searching the bibliographies of all papers. Articles of all languages were reviewed. Thirty-nine studies were identified, however, 13 met the inclusion criteria and thus were included in the analysis

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4. Was the validity of the included studies appraised?

Yes. The quality of the methods utilized by each study identified was assessed using a scale which quantified the likelihood of bias of the trial based upon the description of the randomization, blinding, and patient withdrawals. The article did not indicate the score (if any) that was needed to be attained in order for a study to be included in the analysis.

5. Were assessments of studies reproducible?

Yes. The meta-analysis used the chi-square test although the specific type of test used was not identified. This test for heterogeneity was significant indicating statistical heterogeneity amongst the trials. The heterogeneity was due to one study in particular. When study was excluded, homogeneity between the remaining 12 studies was found. No further tests for heterogeneity were undertaken.

What were the Results?

1. How large was the treatment effect?

Thirty-nine studies were identified, however only 13 met the inclusion criteria for meta-analysis. There were 796 patients enrolled in the 13 studies, 10 trials reported benefits with garlic, while 3 found no difference as compared to placebo. Overall, the meta-analysis revealed that garlic significantly ($p < 0.01$) reduced total cholesterol levels. Treatment with garlic resulted in a 5.8% reduction in total cholesterol levels from baseline. The authors did not report the reduction in cholesterol levels that occurred with placebo. The authors also evaluated the effect of garlic on total cholesterol levels using the 12 homogenous studies and found a smaller (4.3%) reduction in cholesterol levels with garlic. Gastrointestinal symptoms and garlic breath were the most frequently reported adverse effects. It is unclear

if there were significant differences in the incidence of adverse effects between the garlic and placebo groups.

2. How precise were the results?

Among the 13 studies included, treatment with garlic resulted in a 5.8% reduction in total cholesterol levels from baseline. The weighted mean difference was -0.41 mmol/L (95% CI, -0.66 to -0.15 mmol/L). Among the 12 homogenous studies, the reduction in total cholesterol levels with garlic was 4.3%, equivalent to a mean difference of -0.30 mmol/L (95% CI, -0.48 to -0.11 mmol/L).

3. How much does allowance for uncertainty change the results?

Two sensitivity analyses were performed. The first analysis utilized 5 methodologically similar studies (i.e. same garlic preparation, same dose and also controlled for dietary factors). No significant difference in the reduction of total cholesterol with garlic (as compared to placebo) was found. The second analysis included 6 of diet-controlled studies and, once again, the authors found no significant difference between garlic and placebo in the reduction of cholesterol.

Will the Results Help Me in Caring for My Patients?

1. Can the results be applied to my patient care?

No. While the current meta-analysis found garlic to reduce total cholesterol levels by at best 5.8%, there are numerous unanswered questions, which make applying the results of this trial to direct patient care difficult. The reduction in cholesterol levels seen with garlic is considerably less than that seen with other effective lipid-lowering interventions, such as diet or the HMG-CoA reductase inhibitors. Furthermore, it is

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unclear from this analysis of the effect of garlic on other endpoints that are more relevant than total cholesterol levels such as the incidence of coronary heart disease, mortality, and morbidity. While this analysis included all patients with elevated total cholesterol levels, it is unclear whether specific groups of patients would derive greater benefit (i.e. those with or without CHD, elevated low-density lipoprotein, or low high-density lipoprotein. It is also unclear as to the length of therapy required with garlic to derive a 5.8% reduction. The duration of therapy of the studies included in the meta-analysis ranged from 8 weeks to 24 weeks. The benefits of longer therapy are unknown.

2. Were all clinically important outcomes considered?

No. While the use of total cholesterol as a study endpoint is easily measured, it is not the most relevant endpoint to evaluate. Future studies should focus on clinically relevant endpoints, such as the effects of garlic on the specific lipoproteins, such as the atherogenic low-density lipoprotein or high-density lipoprotein, or clinical outcomes, for example total mortality, the incidence of CHD, or death from myocardial infarction and/or CHD.

3. Are the benefits worth the harms and costs?

No. The benefit of garlic in reducing cholesterol levels, in the absence of other relevant clinical endpoints, is likely not worth the costs, despite the minimal adverse effects observed. Lipid-lowering diets are more cost effective than garlic. Furthermore, patients can derive greater cholesterol reductions with diet therapy alone.

Commentary

Cardiovascular disease, of which CHD is the most common, is the leading cause of death in Canada.

Elevated cholesterol is an independent risk factor for heart disease. Numerous studies have shown that the incidence of coronary heart disease and elevated cholesterol to be continuous and graded. Numerous large, randomized, controlled trials have shown that reducing cholesterol levels with HMG-CoA reductase inhibitors, in patients with and without CHD, and with elevated and "average" cholesterol levels reduces mortality and morbidity. In addition to knowing which patients derive the greatest benefit from therapy, the duration of therapy required to obtain benefits, the side effects from these medications are known, and for the most part, minimal. In order to be considered an "alternative" to standard therapies, studies evaluating other forms of lipid-lowering interventions, such as garlic, need to evaluate clinically relevant endpoints, as have the HMG-CoA reductase trials. In the absence of these studies, recommending these "alternative" interventions is difficult. Numerous unanswered questions exist from the current meta-analysis on the use of garlic in reducing total cholesterol levels. As previously mentioned, there are no data on the effect of garlic on the incidence of coronary heart disease, reductions in fatal or non-fatal myocardial infarctions, hospital admissions, or total mortality. Furthermore, it is unclear which types of patients derive the greatest benefit. The meta-analysis included patients with and without CHD and children. The form of garlic administered to patients enrolled in the studies varied from essential oil to standardized powder, or spray-dried powder. Whether there are differences in endpoints based upon the form of garlic used is unknown. Furthermore, the dose of garlic required is unknown. Patients inquiring about the use of garlic for reducing cholesterol should be informed of the minimal reduction in cholesterol levels observed in clinical trials and the aforementioned pitfalls of the current literature. Future randomized, controlled studies of garlic, should evaluate specific groups of patients, specific garlic preparations and doses, and evaluate clinically important endpoints.

J Inform Pharmacother 2000;3:209-211.

Issues in Pharmacotherapy Practice

The Role of Low-Molecular-Weight Heparin for DVT Prophylaxis in Acutely Ill Medical Patients

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Abstract

Background: The majority of pulmonary embolism mortality occurs in the acutely ill medical patient, thus it is of paramount importance to consider prophylaxis against venous thromboembolism in this population. The goal of this paper was to conduct a systematic review of the published literature to delineate the role of the low-molecular-weight heparins (LMWH) compounds for deep vein thrombosis (DVT) prophylaxis in acutely ill medical patients.

Methods: A MEDLINE search (July 1966 - May 2000) was conducted to identify all randomized, controlled trials comparing LMWH to control or to low-dose unfractionated heparin (UFH) in hospitalized medical patients that reported the incidence of venous thrombosis as the primary outcome. Studies that were non-randomized, assessed danaparoid or other heparinoids, or included predominately patients with acute stroke, myocardial infarction or spinal cord injury were excluded from the analysis.

Results: Three studies involving a comparison of LMWH to placebo in a variety of acutely ill medical populations were identified. Patients not receiving LMWH prophylaxis experienced a high incidence of venous thrombosis (14-28%) as compared to those patients receiving thromboprophylaxis with a LMWH (5.5-15.5%). The investigators of eight studies involving a comparison of UFH versus LMWH found no difference in the incidence of venous thrombosis (DVT or pulmonary embolus) or mortality between these groups. The use of LMWH was associated with a lower reported incidence of both major hemorrhage and thrombocytopenia as compared to that reported for UFH therapy.

Conclusions: Acutely ill medical patients, particularly those with risk factors for venous thrombosis, should receive thromboprophylactic therapy. Low-molecular-weight heparin therapy appears to be no more effective than UFH therapy, but may be associated with fewer adverse drug events such as major bleeding.

J Inform Pharmacother 2000;3:300-308.

Introduction

Prevention of thromboembolic disease in hospitalized patients is an important therapeutic issue, as venous thromboembolic disease has become a major public health concern. Although 10% of hospitalized patient deaths can be attributed to pulmonary embolism, only 25% of these deaths occur in the surgical population. The majority of pulmonary embolism mortality occurs in the acutely ill medical patient, thus it is of paramount importance to consider prophylaxis against venous thromboembolism in this population. (1)

The incidence of venous thromboembolic disease has been well documented in medical patients and ranges from 10-26% in epidemiological studies to 33% in autopsy-based studies. (2-8) The risk of venous thrombosis is greatest in patients with known risk factors. In particular, venous thrombosis has been reported to occur in approximately 24% of patients with a myocardial infarction, 42% of patients experiencing a stroke, and as high as 33% of patients admitted to the medical intensive care unit. (1,4,9,10) Other risk factors for venous thromboembolic disease in medical patients include intrinsic factors such as age, obesity, history of venous thromboembolism, and extrinsic factors such as immobilization, cancer, cardiac or respiratory failure, myocardial infarction, paralytic stroke and severe infectious diseases. (4) Various classification systems have also been developed to objectively assess and categorize (i.e. low, moderate or high) the risk of venous thromboembolic risk in medical patients. (1,9)

While extensive clinical benefit and cost-effectiveness data exist to support the routine use of thromboprophylaxis in surgical patients (1), the routine use of thromboprophylaxis against venous thrombosis in general medical patients

remains controversial. (11,12) While certain high-risk medical groups (e.g. paralytic stroke or myocardial infarction) should receive pharmacological prophylaxis, the situation remains less clear for the majority of hospitalized medical patients. (1,11,12)

Until recently, the literature pertaining to the prevention of venous thrombosis in acutely ill medical patients has been relatively sparse. While more than 100,000 surgical patients have been enrolled in venous thrombosis prophylaxis trials, less than 10,000 medical patients have participated in studies of this nature. (13) Furthermore, those published DVT prophylaxis studies that have involved medical patients have been limited by significant methodological heterogeneity including study design, baseline risk factors for venous thrombosis, and the detection methods employed to identify venous thrombosis.

Unfractionated heparin (UFH) is considered the reference antithrombotic agent for the prevention of venous thromboembolic disease in medical patients. When compared to placebo in moderate-risk hospitalized patients, this drug has been shown to reduce the incidence of venous thrombosis from 10%-26% to 2%-4%. In high-risk patients following myocardial infarction, the incidence of venous thromboembolic disease is reduced from 24% to 7%, while in ischemic stroke patients the incidence of this disease is reduced from 42% to 26%. (1,5,14,15)

Over the last 10 years, the use of LMWH agents to prevent or treat venous thromboses has increased. Low-molecular-weight heparins have a number of potential advantages over UFH which include once daily administration, lower incidence of heparin-induced thrombocytopenia, less laboratory monitoring (although aPTT monitoring is not required, periodic CBC monitoring should still be undertaken), and possibly fewer bleeding complications. (16,17)

Numerous controlled studies have shown LMWH to be more effective than other thromboprophylactic strategies such as UFH or warfarin in various surgical populations, particularly orthopedic and trauma patients. (1,18) The incidence of bleeding in some of these surgical studies; however, has been reported to be higher in the LMWH-treated patients. (18) Despite the significantly greater acquisition cost of LMWH as compared to alternatives such as UFH, one U.S.-based pharmacoeconomic study involving trauma patients has demonstrated that LMWH compounds can be more cost-effective than other antithrombotic alternatives. (19)

Several recent reports of large randomized controlled trials involving comparisons of LMWH compounds versus placebo or UFH in acutely ill medical patients have been published. (6-8,20-27) The outcomes studied in these trials have included venous thrombosis (i.e. DVT and PE), drug-related adverse events (i.e. bleeding and thrombocytopenia and patient mortality). A structured review of these studies should help us to delineate the role of the LMWH compounds for DVT prophylaxis in these acutely ill medical patients.

Methods

A MEDLINE literature search for the period July 1966 to May 2000 was completed to identify randomized, controlled trials comparisons of LMWH to UFH or placebo. Only those studies involving LMWH doses equivalent to those recommended by the manufacturer and daily UFH doses of 10,000-15,000 IU (when used as a comparator) were included. Studies that did not involve a recognized method to diagnose deep vein thrombosis (i.e. venography, ultrasonography, impedance phlethysmography, or fibrinogen uptake scanning) were excluded. Non-randomized studies and those studies that involved an assessment of danaparoid or other heparinoids were also excluded. Finally, studies that only assessed LMWH prophylaxis after a stroke, myocardial infarction, or spinal cord injury were also excluded from the analyses.

Results

Placebo-Controlled Trials with Low-Molecular-Weight Heparins

We were able to identify three published randomized controlled studies involving a comparison of a LMWH compound to placebo. (6-8) (Table 1). A double-blind study involving non-surgical elderly patients revealed a 3-fold higher incidence of DVT in the group receiving placebo as compared to the group receiving enoxaparin (9.1% vs. 3.0%, $p < 0.001$). (6) In a subgroup of the placebo-recipients who were also confined to bed, the incidence of DVT was 20%. No patients in the LMWH group experienced a pulmonary embolus (PE), as compared to 3 patients in the placebo arm.

In the Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) trial, 1,102 moderate to high risk medical patients were randomized to receive placebo, enoxaparin 20mg daily or enoxaparin 40mg daily. (7) Study participants had congestive heart failure (New York Heart Association (NYHA) Class III or IV), acute respiratory failure (not requiring ventilatory support), or other specified medical conditions with an additional risk factor for venous thrombosis including age, cancer, previous DVT, or obesity. All patients were examined for lower DVT by systemic ascending contrast

venography between study days 6 and 14, or earlier if a thrombosis was clinically suspected. Possible cases of pulmonary embolism were diagnosed using standard methods. Secondary outcomes included major hemorrhage, heparin-induced thrombocytopenia and death. In this trial, the incidence of venous thrombosis was significantly lower in the group that received 40 mg of enoxaparin (5.5%) as compared to the group that received placebo (14.9%) (relative risk [RR] 0.37, 97.6% confidence interval [CI], 0.22 to 0.63, $p < 0.001$). There was; however, no difference in outcomes between the enoxaparin 20 mg (15.0%, 43 of 287 patients) and placebo groups. In addition, the incidence of adverse events such as major hemorrhage and heparin-induced thrombocytopenia did not differ between groups.

The third placebo-controlled study identified involved 223 mechanically-ventilated patients with chronic obstructive pulmonary disease. (8) These patients were randomized to receive either daily subcutaneous nadroparin (3,800 anti-Xa IU for patients less than 70 kg; 5,700 anti-Xa IU for patients over 70 kg) or placebo. Therapy was continued until the patient was successfully weaned from mechanical ventilation. Only 169 of 221 (76.4%) patients were assessed at study completion using venography. The incidence of total DVT was significantly lower in patients receiving nadroparin than those receiving placebo (15.5% versus 28.2%, respectively, $p = 0.045$). No patients in either treatment arm had a confirmed pulmonary embolus. Neither the incidence of serious hemorrhage (6 patients in the nadroparin arm vs. 3 in the placebo arm) nor thrombocytopenia (10 patients in the nadroparin arm vs. 7 in the placebo arm) differed significantly between groups.

The results of these three studies demonstrate that acutely ill medical patients are at significant risk for developing venous thrombosis during hospitalization. Use of prophylaxis with at least a moderate dose LMWH (i.e. >4000 anti-Xa IU/day) safely appears to decrease the incidence of venous thrombosis in these patients compared to placebo.

Table 1. Trials Comparing Low-Molecular-Weight Heparins to Placebo in Acutely Ill Medical Patients

Author	LMWH	Patients	DVT		PE		Death		Major Bleed	
			LMWH	Control	LMWH	Control	LMWH	Control	LMWH	Control
Dahan 1986 (6)	Enoxaparin (6300 IU/d) x 10 days	N = 270 Various and elderly	4/132	12/131	0/135	3/135	1/135	6/135	1/135	3/135
MEDENOX 1999 (7)	Enoxaparin (40 mg/d) until DC	N = 1120 CHF, COPD, or other major risk	43/287 ^A 16/291 ^B	40/288	0/287 ^A 0/291 ^B	2/288	15/351 ^A 12/360 ^B	16/362	1/351 ^A 6/360 ^B	4/362
Fraisse 2000 (8)	Nadroparin 4100-6150 IU/d ^C until weaned	N = 221 COPD requiring mechanical ventilation	13/84	24/85	0/108	0/113	18/108	17/113	6/108	3/113

^AEnoxaparin 20mg sc daily

^BEnoxaparin 40mg sc daily

^CAdjusted to body weight (45-70kg: 3800 IU; 71-110kg: 5700 IU)

Studies Comparing Unfractionated Heparin with Low-Molecular-Weight Compounds

Eight clinical trials were identified involving 4,085 acutely ill medical patients who received prophylaxis with low dose UFH (up to 15,000 IU heparin/day) versus a LMWH. (20-27) Early mortality was studied as an endpoint in all trials and clinical evidence of PE was assessed in six trials (4033 patients). (Table 2)(20,22,23,25,27)

Two early studies involving a comparison of UFH (10,000-15,000 IU/day) with nadroparin or dalteparin, respectively, in a population of heterogeneous medical patients, showed no significant difference in the incidence of DVT between groups. (20,21) The incidence of DVT was relatively low (<4%) in each group, as compared to the incidence range (5%-16%) reported for patients receiving LMWH in other placebo-controlled studies. (7,8) While the latter study (21) used serial impedance plethysmography (IPG) in addition to ultrasonography to detect deep vein thrombosis, it is unlikely that the combined use of both detection methods would lead to the detection of additional DVT as the sensitivity of each detection method is similar, and evidence does not suggest that sensitivity of either method is improved, particularly in asymptomatic patients, when used together. (28)

The HESIM Group, have conducted the largest published study comparing LMWH to UFH to date. (23) This trial examined the incidence of venous thrombosis, mortality, and bleeding-related outcomes in 1,590 medical inpatients who were

randomized to receive either subcutaneous UFH 5,000 IU three times daily or nadroparin 36 mg once daily. All subjects were medical inpatients with an identifiable risk for venous thrombosis. The incidence of thromboembolic events (i.e. combined proximal DVT and PE) did not differ between treatment groups (4 in the UFH group vs. 6 in the with LMWH, $p = 0.12$). There were 32 deaths in study patients. Nine of these patients had been randomized to UFH therapy, while 23 received LMWH therapy ($p = 0.02$). The incidence of major hemorrhage was low and did not differ between groups. Four patients in the UFH group developed thrombocytopenia (platelets $<80,000/\mu\text{L}$) compared to none in the nadroparin-treated patient group. The low incidence of venous thrombosis in this study population was also attributed to the low sensitivity of compression sonography in asymptomatic patients. (29,30)

Three studies have been published that involved a comparison of enoxaparin (20 to 40 mg per day) with UFH (10,000–15,000 IU per day) in a variety of acutely ill medical populations. (25–27) PRIME randomized 959 hospitalized medical patients to enoxaparin 40mg daily or UFH 5000 IU three times daily. (25) There was no significant difference between any of the study outcomes (DVT, PE, death, or major bleeding) although there was a trend in the UFH treated group towards an increased incidence of PE [4/482 (0.008%) UFH versus 0/477 (0%) enoxaparin] and major bleeds [9/482 (0.02%) UFH versus 2/477 (0.004%) enoxaparin].

The Enoxaparin in Medicine Study Group (EMSG) conducted in a double-blind study involving a comparison of enoxaparin 20mg daily with UHF 5000 IU twice daily in 439 elderly, hospitalized patients who were bedridden for an acute medical illness. (26) The incidence of DVT in the enoxaparin group [10/207 (4.8%)] was equivalent to that of the UFH group [10/216 (4.6%)]. No difference in the incidence of bleeding complications or mortality was found between the groups.

The Thromboembolism Prevention in Cardiopulmonary Diseases with Enoxaparin (PRINCE) group, compared UFH 5000 IU three times daily to enoxaparin 40 mg daily in 668 medical patients admitted to hospital with either heart failure (NYHA Class III or IV) or severe respiratory disease. (27) Similar to other studies, (7,26) not all randomized patients were available for serial assessment for venous thrombosis by venography. This was reported to be typically due to patient refusal, technical problems or death. The number of thromboembolic events was not significantly different between the enoxaparin (8.4%) and UFH (10.8%) - treated patients. In the subgroup of patients with heart failure; however, the incidence of thromboembolic events was significantly higher in the UFH group (16.1% versus 9.7%). (31) Adverse events including bleeding complications (3.6% heparin vs. 1.5% enoxaparin and injection site hematomas (12.6% heparin vs. 7.2% enoxaparin) appeared to be more common in the UFH treatment arm. (27)

A recent meta-analysis has been published that involves an assessment of these eight trials, in combination with another trial (32) that was conducted to primarily evaluated the incidence of PE in medical patients. The authors of this study found no difference between the efficacy of LMWH versus UFH therapy. (13) When comparing LMWH to UFH therapy, the incidence of DVT (RR 0.83, [95% CI 0.56 to 1.24, $p = 0.37$), clinical PE (RR 0.74, [95% CI 0.29 to 1.88], $p = 0.52$), and mortality (RR 1.07, [95% CI 0.79 to 1.45], $p = 0.66$) did not differ between treatment groups. LMWH therapy; however, was associated with a lower incidence of major hemorrhage (RR 0.48, [95% CI 0.23 to 1.00], $p = 0.049$).

Table 2. Trials Comparing Low Molecular Weight Heparins to Unfractionated Heparin in Acutely Ill Medical Patients

Author	LMWH/UFH	Patients	DVT		PE		Death		Major Bleed	
			LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH
Aquino 1990 (20)	Nadroparin 3075 IU vs. UFH 10000–15000 U x 10d	N = 99 Various and elderly	1/49	1/50	0/49	0/50	1/49	2/50	0/49	2/50
Haremborg 1990 (21)	Dalteparin 2500 IU vs. UFH 15000 IU x 10d	N = 166 Various	3/84	4/82	N/A	N/A	3/84	1/82	0/84	1/82
Forette 1995 (22)	Nadroparin 3075 IU vs. UFH* 10,000–15000 IU x 28d	N = 295 Various and elderly	3/146	3/149	0/146	1/149	6/146	7/149	0/146	4/149
HESIM 1996 (23)	Nadroparin 3100 IU vs. UFH 15000 IU x 10d	N = 1590 Elderly and expected bed rest > 10 days (with additional DVT risk factor)	6/726	4/710	5/810	6/780	23/810	9/780	5/810	4/780

APTE 1996 (24)	Nadroparin 3075 IU vs. UFH 10000 IU x 90d	N = 256 Various and elderly	0/129	1/127	N/A	N/A	8/129	8/127	1/129	4/127
PRIME 1996 (25)	Enoxaparin 4000 IU vs. UFH 15000 IU x 7d	N = 959 Various and elderly	1/477	4/482	0/477	4/482	7/477	11/482	2/477	9/482
EMSG 1996 (26)	Enoxaparin 2100 IU vs. UFH 10000 IU x 10d	N = 439 Various and elderly	10/207	10/216	1/216	0/223	7/216	8/223	1/216	2/223
PRINCE 1998 (27)	Enoxaparin 4200 IU vs. UFH 15000 IU x 10d	N = 665 Cardiopulmonary disease (confined to bed; expected hospitalization for > 1 wk)	19/239	22/212	1/239	1/212	28/332	30/333	1/332	1/333

* Adjusted to body weight (40-70kg: 10,000u; > 70kg: 15,000u)

Discussion

Pooled analysis of available studies demonstrates that the baseline risk for lower extremity DVT in acutely ill medical patients is approximately 19%. (13) This incidence is comparable to that observed in general surgery patients, but less than that observed in patients after acute ischemic stroke or orthopedic surgery. (1) The results from the meta-analysis demonstrate a 56% decrease in DVT when either LMWH or UFH is administered to acutely ill medical patients. (13) This decrease is similar to the risk reduction observed in many other medical or surgical populations. (1)

Studies comparing LMWH or UFH to placebo are important to review because they help to establish the magnitude of venous thrombosis risk in acutely ill medical patients as well as quantify the effect of LMWH or UFH prophylaxis on this risk. The high incidence of venous thrombosis in patients not receiving prophylaxis underscores the importance of routine assessment of the risk for venous thromboembolism in patients, and the provision of adequate prophylactic therapy. In view of the equivalent efficacy of LMWH to UFH prophylactic therapy observed in each of these trials, however, it is somewhat surprising that these large, placebo-controlled trials could be ethically completed. (7,8,13) Investigators appeared to justify the use of a placebo arm by the fact that the incidence of venous thrombosis among such medical patients has not been established, the lack of a 'gold-standard' method of thromboprophylaxis for these patients, and patients with a very high risk of venous thrombosis (e.g. prolonged immobilization, acute stroke) were excluded from each study. (8) Although low-dose UFH is widely used as prophylaxis against thrombosis, it is not a validated control treatment for medical patients. In fact, the few studies supporting its use have been small, data on mortality is conflicting and the recommendations of consensus conferences are not definitive. (1,5,33-35)

Those trials that involved an evaluation of LMWH versus placebo or UFH versus placebo that are available for analysis reveal that UFH/LMWH therapy significantly decreases the incidence of DVT (RR 0.44, [95% CI 0.29-0.64]; $p < 0.001$) and PE (RR 0.48 [95% 0.34 - 0.64], $p < 0.001$), but does not effect mortality (RR 0.98 [95% CI 0.79 to 1.21], $p = 0.37$). (13) While homogeneity testing in the meta-analysis performed by Mismetti et al. achieved significance, there is still considerable methodological heterogeneity found between studies. (13) These differences between studies may affect the incidence of venous thrombosis reported. The reported incidence of venous thrombosis depends not only on the prevalence of the disease, but also on the sensitivity and specificity of the diagnostic test that is used to detect it. In general, clinical symptoms suggestive of a DVT are only present in approximately 50% of patients actually having venous thrombosis. (36) In these patients, venography remains the 'gold standard' diagnostic test. However, the need for irradiation, the invasiveness of the test, and the potential to induce thrombosis, all limit the use of venography in clinical practice - particularly for those patients deemed to be at low or moderate risk for developing venous thrombosis. (37) Despite its expense and complicity, venography remains the reference method of choice for screening for deep-vein thrombosis in asymptomatic patients. Many of the older studies used other diagnostic methods to detect DVT such as fibrinogen uptake testing, impedance phlethysmography, or ultrasonography whose sensitivity in asymptomatic patients is low. (29,30)

Most of the DVT detected in the reviewed studies were asymptomatic in nature and/or distal in location. (6-8,20-27) This diagnosis led to the initiation of full-dose anticoagulation therapy in many patients. The low propensity of distal DVT to propagate more proximally (e.g. to the lungs) and the potential risks of anticoagulation therapy must be considered when evaluating the results of each study. (37-39) In clinical practice, few asymptomatic medical patients would be routinely screened for the presence of DVT. Furthermore, at most institutions, duplex ultrasound rather than the significantly more sensitive venography, would be the screening test of choice for all patients regardless of

symptomatology. It remains unclear from these studies how patient outcome would have differed with respect to both incidence of venous thrombosis and mortality had only symptomatic patients been screened and treated if a venous thrombosis was detected. The pooled studies, however, demonstrated a 52% risk reduction in clinical and fatal PE with the use of UFH or LMWH. (13) This fact alone, regardless of the incidence and anatomical location of the DVT that was detected, provides the clinician with strong evidence to consider the use of either of these heparin agents as prophylaxis in clinical practice.

In each of the studies reviewed, there was a significant number of patients that were not able to be assessed. (6-8, 31-38) For example, in the MEDENOX study, 22% of the patients who were randomized into the study were not included in the analysis mostly because of the clinical difficulty in completing venography in these patients. (7) These, in fact, may be patients who are at a relatively higher risk for venous thrombosis. The inability to assess these patients may have lead to an underestimation of the treatment effect of enoxaparin.

Although the pooled results of available studies suggests that hospitalized medical patients should be considered for prophylactic therapy with either UFH or a LMWH compound, some of the studies, when reviewed individually, do not support this recommendation. (6,13) This is mainly due to the fact that the baseline risk for venous thrombosis has varied greatly among studies. (6,7,33) For example, in some studies, patients were confined to bed while in other trials, the majority of patients were ambulant. (7) In addition, some studies included only mechanically ventilated, medical ICU patients, whereas others excluded this high-risk population. (6,8,21)

The negative trials were also characterized by a short duration of thromboprophylaxis. (20,21,25,32) For example, in the MEDENOX study, two fatal pulmonary emboli occurred in the enoxaparin 40 mg treatment group several weeks after prophylaxis had been discontinued. (7) Any conclusions regarding the impact of either of these therapeutic modalities on patient mortality has to be carefully assessed on a study-by-study basis. It is also important to note that many of the studies were not powered to detect a difference in clinical outcomes such as mortality. (5,6,20-22,24,33) While three studies have assessed the ability of thromboprophylaxis to decrease mortality in acutely ill medical patients, (14,15,34) the results may be questionable based on the short period of follow-up and the various methodological weaknesses of these studies already described.

While the use of LMWH does not appear to be associated with improved clinical outcomes (i.e. venous thrombosis and patient mortality) as compared to UFH, this newer class of drug does appear to be safer. LMWH administration was associated with only half the number of major bleeding episodes compared to UFH-treated patients. (13) This is an interesting finding when we consider that DVT prophylaxis with LMWH in various surgical populations has been associated with a greater incidence of bleeding than that observed with UFH. (18) The lower incidence of bleeding observed in trials involving medical patients may be related to the lower LMWH dose that was administered. After pooling LMWH surgical prophylaxis studies, a clear dose-response effect of LMWH related to bleeding risk has been demonstrated. (40) Patients appear to be at significantly greater risk for experiencing a bleeding episode when the they receive more than 3400 anti-Xa IU of a LMWH per day. An additional safety advantage of using LMWH rather than UFH prophylaxis is the decreased incidence of heparin-induced thrombocytopenia observed with LMWH use. (17)

Low-molecular-weight heparin therapy can be administered on a once daily basis to patients and thereby will potentially decrease drug administration costs compared to the twice or thrice daily dosing regimens used with UFH. However, the significantly greater acquisition costs associated with LMWH therapy is unlikely to offset any administration-related savings. Although a formal pharmacoeconomic analysis of UFH versus LMWH prophylaxis in acutely ill medical patients has yet to be published, economic studies in other populations where UFH and LMWH therapeutic equivalence has been demonstrated (e.g. DVT prophylaxis in general surgery patients) have not revealed LMWH therapy to be cost-effective. (41)

Conclusion

Current literature demonstrates that acutely ill medical patients, (particularly those with respiratory failure or decompensated heart failure), without contraindications to therapy (e.g. active bleeding), should receive pharmacologic thromboprophylaxis. Substantial evidence now demonstrates that LMWH prophylaxis to be no more efficacious than UFH, except perhaps in patients with decompensated CHF. A decreased incidence of heparin-related adverse events (i.e. bleeding and thrombocytopenia) and the opportunity for once-daily dosing is certainly enticing, but is still unlikely to make LMWH a cost-effective alternative (over UFH) for DVT prophylaxis in acutely ill medical patients. Further LMWH versus UFH studies are needed in higher risk medical patients (e.g. mechanically ventilated MICU patients) to further delineate any advantages that this newer class of drugs may have in this population.

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The Role of Low-Molecular-Weight Heparin for DVT Prophylaxis in Acutely Ill Medical Patients

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Background: The majority of pulmonary embolism mortality occurs in the acutely ill medical patient, thus it is of paramount importance to consider prophylaxis against venous thromboembolism in this population. The goal of this paper was to conduct a systematic review of the published literature to delineate the role of the low-molecular-weight heparins (LMWH) compounds for deep vein thrombosis (DVT) prophylaxis in acutely ill medical patients.

Methods: A MEDLINE search (July 1966 - May 2000) was conducted to identify all randomized, controlled trials comparing LMWH to control or to low-dose unfractionated heparin (UFH) in hospitalized medical patients that reported the incidence of venous thrombosis as the primary outcome. Studies that were non-randomized, assessed danaparoid or other heparinoids, or included predominately patients with acute stroke, myocardial infarction or spinal cord injury were excluded from the analysis.

Results: Three studies involving a comparison of LMWH to placebo in a variety of acutely ill medical populations were identified. Patients not receiving LMWH prophylaxis experienced a high incidence of venous thrombosis (14-28%) as compared to those patients receiving thromboprophylaxis with a LMWH (5.5-15.5%). The investigators of eight studies involving a comparison of UFH versus LMWH found no difference in the incidence of venous thrombosis (DVT or pulmonary embolus) or mortality between these groups. The use of LMWH was associated with a lower reported incidence of both major hemorrhage and thrombocytopenia as compared to that reported for UFH therapy.

Conclusions: Acutely ill medical patients, particularly those with risk factors for venous thrombosis, should receive thromboprophylactic therapy. Low-molecular-weight heparin therapy appears to be no more effective than UFH therapy, but may be

associated with fewer adverse drug events such as major bleeding.

J Inform Pharmacother 2000;3:300-308.

Prevention of thromboembolic disease in hospitalized patients is an important therapeutic issue, as venous thromboembolic disease has become a major public health concern. Although 10% of hospitalized patient deaths can be attributed to pulmonary embolism, only 25% of these deaths occur in the surgical population. The majority of pulmonary embolism mortality occurs in the acutely ill medical patient, thus it is of paramount importance to consider prophylaxis against venous thromboembolism in this population. (1)

The incidence of venous thromboembolic disease has been well documented in medical patients and ranges from 10-26% in epidemiological studies to 33% in autopsy-based studies. (2-8) The risk of venous thrombosis is greatest in patients with known risk factors. In particular, venous thrombosis has been reported to occur in approximately 24% of patients with a myocardial infarction, 42% of patients experiencing a stroke, and as high as 33% of patients admitted to the medical intensive care unit. (1,4,9,10) Other risk factors for venous thromboembolic disease in medical patients include intrinsic factors such as age, obesity, history of venous thromboembolism, and extrinsic factors such as immobilization, cancer, cardiac or respiratory failure, myocardial infarction, paralytic stroke and severe infectious diseases. (4) Various classification systems have also been developed to objectively assess and categorize (i.e. low, moderate or high) the risk of venous thromboembolic risk in medical patients. (1,9)

While extensive clinical benefit and cost-effectiveness data exist to support the routine use of

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thromboprophylaxis in surgical patients (1), the routine use of thromboprophylaxis against venous thrombosis in general medical patients remains controversial. (11,12) While certain high-risk medical groups (e.g. paralytic stroke or myocardial infarction) should receive pharmacological prophylaxis, the situation remains less clear for the majority of hospitalized medical patients. (1,11,12)

Until recently, the literature pertaining to the prevention of venous thrombosis in acutely ill medical patients has been relatively sparse. While more than 100,000 surgical patients have been enrolled in venous thrombosis prophylaxis trials, less than 10,000 medical patients have participated in studies of this nature. (13) Furthermore, those published DVT prophylaxis studies that have involved medical patients have been limited by significant methodological heterogeneity including study design, baseline risk factors for venous thrombosis, and the detection methods employed to identify venous thrombosis.

Unfractionated heparin (UFH) is considered the reference antithrombotic agent for the prevention of venous thromboembolic disease in medical patients. When compared to placebo in moderate-risk hospitalized patients, this drug has been shown to reduce the incidence of venous thrombosis from 10%-26% to 2%-4%. In high-risk patients following myocardial infarction, the incidence of venous thromboembolic disease is reduced from 24% to 7%, while in ischemic stroke patients the incidence of this disease is reduced from 42% to 26%. (1,5,14,15)

Over the last 10 years, the use of LMWH agents to prevent or treat venous thromboses has increased. Low-molecular-weight heparins have a number of potential advantages over UFH which include once daily administration, lower incidence of heparin-induced thrombocytopenia, less laboratory monitoring (although aPTT monitoring is not required, periodic CBC monitoring should still be undertaken), and possibly fewer bleeding complications. (16,17)

Numerous controlled studies have shown LMWH to be more effective than other thromboprophylactic strategies such as UFH or warfarin in various surgical populations, particularly orthopedic and trauma patients. (1,18) The incidence of bleeding in some of

these surgical studies; however, has been reported to be higher in the LMWH-treated patients. (18) Despite the significantly greater acquisition cost of LMWH as compared to alternatives such as UFH, one U.S.-based pharmacoeconomic study involving trauma patients has demonstrated that LMWH compounds can be more cost-effective than other antithrombotic alternatives. (19)

Several recent reports of large randomized controlled trials involving comparisons of LMWH compounds versus placebo or UFH in acutely ill medical patients have been published. (6-8,20-27) The outcomes studied in these trials have included venous thrombosis (i.e. DVT and PE), drug-related adverse events (i.e. bleeding and thrombocytopenia and patient mortality). A structured review of these studies should help us to delineate the role of the LMWH compounds for DVT prophylaxis in these acutely ill medical patients.

Methods

A MEDLINE literature search for the period July 1966 to May 2000 was completed to identify randomized, controlled trials comparisons of LMWH to UFH or placebo. Only those studies involving LMWH doses equivalent to those recommended by the manufacturer and daily UFH doses of 10,000-15,000 IU (when used as a comparator) were included. Studies that did not involve a recognized method to diagnose deep vein thrombosis (i.e. venography, ultrasonography, impedance phlethysmography, or fibrinogen uptake scanning) were excluded. Non-randomized studies and those studies that involved an assessment of danaparoid or other heparinoids were also excluded. Finally, studies that only assessed LMWH prophylaxis after a stroke, myocardial infarction, or spinal cord injury were also excluded from the analyses.

Results

Placebo-Controlled Trials with Low-Molecular-Weight Heparins

We were able to identify three published randomized controlled studies involving a comparison of a LMWH compound to placebo. (6-8) (Table 1). A

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Table 1. Trials Comparing Low-Molecular-Weight Heparins to Placebo in Acutely Ill Medical Patients

Author	LMWH	Patients	DVT		PE		Death		Major Bleed	
			LMWH	Control	LMWH	Control	LMWH	Control	LMWH	Control
Dahan 1986 (6)	Enoxaparin (6300 IU/d) x 10 days	N = 270 Various and elderly	4/132	12/131	0/135	3/135	1/135	6/135	1/135	3/135
MEDENOX 1999 (7)	Enoxaparin (40 mg/d) until DC	N = 1120 CHF, COPD, or other major risk	43/287 ^A 16/291 ^B	40/288	0/287 ^A 0/291 ^B	2/288	15/351 ^A 12/360 ^B	16/362	1/351 ^A 6/360 ^B	4/362
Fraisse 2000 (8)	Nadroparin 4100-6150 IU/d ^C until weaned	N = 221 COPD requiring mechanical ventilation	13/84	24/85	0/108	0/113	18/108	17/113	6/108	3/113

^AEnoxaparin 20mg sc daily

^BEnoxaparin 40mg sc daily

^CAdjusted to body weight (45-70kg: 3800 IU; 71-110kg: 5700 IU)

double-blind study involving non-surgical elderly patients revealed a 3-fold higher incidence of DVT in the group receiving placebo as compared to the group receiving enoxaparin (9.1% vs. 3.0%, $p < 0.001$). (6) In a subgroup of the placebo-recipients who were also confined to bed, the incidence of DVT was 20%. No patients in the LMWH group experienced a pulmonary embolus (PE), as compared to 3 patients in the placebo-arm.

In the Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) trial, 1,102 moderate to high risk medical patients were randomized to receive placebo, enoxaparin 20mg daily or enoxaparin 40mg daily. (7) Study participants had congestive heart failure (New York Heart Association (NYHA) Class III or IV), acute respiratory failure (not requiring ventilatory support), or other specified medical conditions with an additional risk factor for venous thrombosis including age, cancer, previous DVT, or obesity. All patients were examined for lower DVT by systemic ascending contrast venography between study days 6 and 14, or earlier if a thrombosis was clinically suspected. Possible cases of pulmonary embolism were diagnosed using standard methods. Secondary outcomes included major hemorrhage, heparin-induced thrombocytopenia and death. In this trial, the incidence of venous thrombosis was significantly lower in the group that received 40 mg of enoxaparin (5.5%) as compared to the group that received

placebo (14.9%) (relative risk [RR] 0.37, 97.6%confidence interval [CI], 0.22 to 0.63, $p < 0.001$). There was; however, no difference in outcomes between the enoxaparin 20 mg (15.0%, 43 of 287 patients) and placebo groups. In addition, the incidence of adverse events such as major hemorrhage and heparin-induced thrombocytopenia did not differ between groups.

The third placebo-controlled study identified involved 223 mechanically-ventilated patients with chronic obstructive pulmonary disease. (8) These patients were randomized to receive either daily subcutaneous nadroparin (3,800 anti-Xa IU for patients less than 70 kg; 5,700 anti-Xa IU for patients over 70 kg) or placebo. Therapy was continued until the patient was successfully weaned from mechanical ventilation. Only 169 of 221 (76.4%) patients were assessed at study completion using venography. The incidence of total DVT was significantly lower in patients receiving nadroparin than those receiving placebo (15.5% versus 28.2%, respectively, $p = 0.045$). No patients in either treatment arm had a confirmed pulmonary embolus. Neither the incidence of serious hemorrhage (6 patients in the nadroparin arm vs. 3 in the placebo arm) nor thrombocytopenia (10 patients in the nadroparin arm vs. 7 in the placebo arm) differed significantly between groups.

The results of these three studies demonstrate that acutely ill medical patients are at significant risk for

developing venous thrombosis during hospitalization. Use of prophylaxis with at least a moderate dose LMWH (i.e. >4000 anti-Xa IU/day) safely appears to decrease the incidence of venous thrombosis in these patients compared to placebo.

Studies Comparing Unfractionated Heparin with Low-Molecular-Weight Compounds

Eight clinical trials were identified involving 4,085 acutely ill medical patients who received prophylaxis with low dose UFH (up to 15,000 IU heparin/day) versus a LMWH. (20-27) Early mortality was studied as an endpoint in all trials and clinical evidence of PE was assessed in six trials (4033 patients). (Table 2)(20,22,23,25,27)

Two early studies involving a comparison of UFH (10,000-15,000 IU/day) with nadroparin or dalteparin, respectively, in a population of heterogeneous medical patients, showed no significant difference in the incidence of DVT between groups. (20,21) The incidence of DVT was relatively low (<4%) in each group, as compared to the incidence range (5%-16%) reported for patients receiving LMWH in other placebo-controlled studies. (7,8) While the latter study (21) used serial impedance plethysmography (IPG) in addition to ultrasonography to detect deep vein thrombosis, it is unlikely that the combined use of both detection methods would lead to the detection of additional DVT as the sensitivity of each detection method is similar, and evidence does not suggest that sensitivity of either method is improved, particularly in asymptomatic patients, when used together.(28)

The HESIM Group, have conducted the largest published study comparing LMWH to UFH to date. (23) This trial examined the incidence of venous thrombosis, mortality, and bleeding-related outcomes in 1,590 medical inpatients who were randomized to receive either subcutaneous UFH 5,000 IU three times daily or nadroparin 36 mg once daily. All subjects were medical inpatients with an identifiable risk for venous thrombosis. The incidence of thromboembolic events (i.e. combined proximal DVT and PE) did not differ between treatment groups (4 in the UFH group vs. 6 in the with LMWH, $p = 0.12$. There were 32 deaths in study patients. Nine of these patients had been randomized to UFH therapy, while 23 received

LMWH therapy ($p = 0.02$). The incidence of major hemorrhage was low and did not differ between groups. Four patients in the UFH group developed thrombocytopenia (platelets <80,000/uL) compared to none in the nadroparin-treated patient group. The low incidence of venous thrombosis in this study population was also attributed to the low sensitivity of compression sonography in asymptomatic patients. (29,30)

Three studies have been published that involved a comparison of enoxaparin (20 to 40 mg per day) with UFH (10,000-15,000 IU per day) in a variety of acutely ill medical populations. (25-27) PRIME randomized 959 hospitalized medical patients to enoxaparin 40mg daily or UFH 5000 IU three times daily. (25) There was no significant difference between any of the study outcomes (DVT, PE, death, or major bleeding) although there was a trend in the UFH treated group towards an increased incidence of PE [4/482 (0.008%) UFH versus 0/477 (0%) enoxaparin] and major bleeds [9/482 (0.02%) UFH versus 2/477 (0.004%) enoxaparin].

The Enoxaparin in Medicine Study Group (EMSG) conducted in a double-blind study involving a comparison of enoxaparin 20mg daily with UHF 5000 IU twice daily in 439 elderly, hospitalized patients who were bedridden for an acute medical illness. (26) The incidence of DVT in the enoxaparin group [10/207 (4.8%)] was equivalent to that of the UFH group [10/216 (4.6%)]. No difference in the incidence of bleeding complications or mortality was found between the groups.

The Thromboembolism Prevention in Cardio-pulmonary Diseases with Enoxaparin (PRINCE) group, compared UFH 5000 IU three times daily to enoxaparin 40 mg daily in 668 medical patients admitted to hospital with either heart failure (NYHA Class III or IV) or severe respiratory disease. (27) Similar to other studies, (7,26) not all randomized patients were available for serial assessment for venous thrombosis by venography. This was reported to be typically due to patient refusal, technical problems or death. The number of thromboembolic events was not significantly different between the enoxaparin (8.4%) and UFH (10.8%) - treated patients. In the subgroup of patients with heart failure; however, the incidence of thromboembolic events was significantly higher in the UFH group 16.1% versus 9.7%). (31) Adverse

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Table 2. Trials Comparing Low Molecular Weight Heparins to Unfractionated Heparin in Acutely Ill

Author	LMWH/UFH	Patients	DVT		PE		Death		Major Bleed	
			LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH
Aquino 1990 (20)	Nadroparin 3075 IU vs. UFH 10000-15000 U x 10d	N = 99 Various and elderly	1/49	1/50	0/49	0/50	1/49	2/50	0/49	2/50
Haremborg 1990 (21)	Dalteparin 2500 IU vs. UFH 15000 IU x 10d	N = 166 Various	3/84	4/82	N/A	N/A	3/84	1/82	0/84	1/82
Forette 1995 (22)	Nadroparin 3075 IU vs. UFH* 10,000-15000 IU x 28d	N = 295 Various and elderly	3/146	3/149	0/146	1/149	6/146	7/149	0/146	4/149
HESIM 1996 (23)	Nadroparin 3100 IU vs. UFH 15000 IU x 10d	N = 1590 Elderly and expected bed rest > 10 days (with additional DVT risk factor)	6/726	4/710	5/810	6/780	23/810	9/780	5/810	4/780
APTE 1996 (24)	Nadroparin 3075 IU vs. UFH 10000 IU x 90d	N = 256 Various and elderly	0/129	1/127	N/A	N/A	8/129	8/127	1/129	4/127
PRIME 1996 (25)	Enoxaparin 4000 IU vs. UFH 15000 IU x 7d	N = 959 Various and elderly	1/477	4/482	0/477	4/482	7/477	11/482	2/477	9/482
EMSG 1996 (26)	Enoxaparin 2100 IU vs. UFH 10000 IU x 10d	N = 439 Various and elderly	10/207	10/216	1/216	0/223	7/216	8/223	1/216	2/223
PRINCE 1998 (27)	Enoxaparin 4200 IU vs. UFH 15000 IU x 10d	N = 665 Cardiopulmonary disease (confined to bed; expected hospitalization for > 1 wk)	19/239	22/212	1/239	1/212	28/332	30/333	1/332	1/333

* Adjusted to body weight (40-70kg: 10,000u; > 70kg: 15,000u)

events including bleeding complications (3.6% heparin vs. 1.5% enoxaparin and injection site hematomas (12.6% heparin vs. 7.2% enoxaparin) appeared to be more common in the UFH treatment arm. (27)

A recent meta-analysis has been published that involves an assessment of these eight trials, in combination with another trial (32) that was conducted to primarily evaluated the incidence of PE in medical patients. The authors of this study found

no difference between the efficacy of LMWH versus UFH therapy. (13) When comparing LMWH to UFH therapy, the incidence of DVT (RR 0.83, [95% CI 0.56 to 1.24, p = 0.37), clinical PE (RR 0.74, [95% CI 0.29 to 1.88], p = 0.52), and mortality (RR 1.07, [95% CI 0.79 to 1.45], p = 0.66) did not differ between treatment groups. LMWH therapy; however, was associated with a lower incidence of major hemorrhage (RR 0.48, [95% CI 0.23 to 1.00], p = 0.049).

Discussion

Pooled analysis of available studies demonstrates that the baseline risk for lower extremity DVT in acutely ill medical patients is approximately 19%. (13) This incidence is comparable to that observed in general surgery patients, but less than that observed in patients after acute ischemic stroke or orthopedic surgery. (1) The results from the meta-analysis demonstrate a 56% decrease in DVT when either LMWH or UFH is administered to acutely ill medical patients. (13) This decrease is similar to the risk reduction observed in many other medical or surgical populations. (1)

Studies comparing LMWH or UFH to placebo are important to review because they help to establish the magnitude of venous thrombosis risk in acutely ill medical patients as well as quantify the effect of LMWH or UFH prophylaxis on this risk. The high incidence of venous thrombosis in patients not receiving prophylaxis underscores the importance of routine assessment of the risk for venous thromboembolism in patients, and the provision of adequate prophylactic therapy. In view of the equivalent efficacy of LMWH to UFH prophylactic therapy observed in each of these trials, however, it is somewhat surprising that these large, placebo-controlled trials could be ethically completed. (7,8,13) Investigators appeared to justify the use of a placebo arm by the fact that the incidence of venous thrombosis among such medical patients has not been established, the lack of a 'gold-standard' method of thromboprophylaxis for these patients, and patients with a very high risk of venous thrombosis (e.g. prolonged immobilization, acute stroke) were excluded from each study. (8) Although low-dose UFH is widely used as prophylaxis against thrombosis, it is not a validated control treatment for medical patients. In fact, the few studies supporting its use have been small, data on mortality is conflicting and the recommendations of consensus conferences are not definitive. (1,5,33-35)

Those trials that involved an evaluation of LMWH versus placebo or UFH versus placebo that are available for analysis reveal that UFH/LMWH therapy significantly decreases the incidence of DVT (RR 0.44, [95% CI 0.29-0.64]; $p < 0.001$) and PE (RR 0.48 [95% 0.34 - 0.64], $p < 0.001$), but does not effect mortality

(RR 0.98 [95% CI 0.79 to 1.21], $p = 0.37$). (13) While homogeneity testing in the meta-analysis performed by Mismetti et al. achieved significance, there is still considerable methodological heterogeneity found between studies. (13) These differences between studies may affect the incidence of venous thrombosis reported. The reported incidence of venous thrombosis depends not only on the prevalence of the disease, but also on the sensitivity and specificity of the diagnostic test that is used to detect it. In general, clinical symptoms suggestive of a DVT are only present in approximately 50% of patients actually having venous thrombosis. (36) In these patients, venography remains the 'gold standard' diagnostic test. However, the need for irradiation, the invasiveness of the test, and the potential to induce thrombosis, all limit the use of venography in clinical practice - particularly for those patients deemed to be at low or moderate risk for developing venous thrombosis. (37) Despite its expense and complicity, venography remains the reference method of choice for screening for deep-vein thrombosis in asymptomatic patients. Many of the older studies used other diagnostic methods to detect DVT such as fibrinogen uptake testing, impedance phlethysmography, or ultrasonography whose sensitivity in asymptomatic patients is low. (29,30)

Most of the DVT detected in the reviewed studies were asymptomatic in nature and/or distal in location. (6-8,20-27) This diagnosis led to the initiation of full-dose anticoagulation therapy in many patients. The low propensity of distal DVT to propagate more proximally (e.g. to the lungs) and the potential risks of anticoagulation therapy must be considered when evaluating the results of each study. (37-39) In clinical practice, few asymptomatic medical patients would be routinely screened for the presence of DVT. Furthermore, at most institutions, duplex ultrasound rather than the significantly more sensitive venography, would be the screening test of choice for all patients regardless of symptomatology. It remains unclear from these studies how patient outcome would have differed with respect to both incidence of venous thrombosis and mortality had only symptomatic patients been screened and treated if a venous thrombosis was detected. The pooled studies, however, demonstrated a 52% risk reduction in clinical and fatal PE with the use of UFH or LMWH. (13) This fact alone, regardless of the incidence and anatomical location of the DVT that was detected, provides the

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clinician with strong evidence to consider the use of either of these heparin agents as prophylaxis in clinical practice.

In each of the studies reviewed, there was a significant number of patients that were not able to be assessed. (6-8, 31-38) For example, in the MEDENOX study, 22% of the patients who were randomized into the study were not included in the analysis mostly because of the clinical difficulty in completing venography in these patients. (7) These, in fact, may be patients who are at a relatively higher risk for venous thrombosis. The inability to assess these patients may have lead to an underestimation of the treatment effect of enoxaparin.

Although the pooled results of available studies suggests that hospitalized medical patients should be considered for prophylactic therapy with either UFH or a LMWH compound, some of the studies, when reviewed individually, do not support this recommendation. (6,13) This is mainly due to the fact that the baseline risk for venous thrombosis has varied greatly among studies. (6,7,33) For example, in some studies, patients were confined to bed while in other trials, the majority of patients were ambulant. (7) In addition, some studies included only mechanically ventilated, medical ICU patients, whereas others excluded this high-risk population. (6,8,21)

The negative trials were also characterized by a short duration of thromboprophylaxis. (20,21,25,32) For example, in the MEDENOX study, two fatal pulmonary emboli occurred in the enoxaparin 40 mg treatment group several weeks after prophylaxis had been discontinued. (7) Any conclusions regarding the impact of either of these therapeutic modalities on patient mortality has to be carefully assessed on a study-by-study basis. It is also important to note that many of the studies were not powered to detect a difference in clinical outcomes such as mortality. (5,6,20-22,24,33) While three studies have assessed the ability of thromboprophylaxis to decrease mortality in acutely ill medical patients, (14,15,34) the results may be questionable based on the short period of follow-up and the various methodological weaknesses of these studies already described.

While the use of LMWH does not appear to be associated with improved clinical outcomes (i.e.

venous thrombosis and patient mortality) as compared to UFH, this newer class of drug does appear to be safer. LMWH administration was associated with only half the number of major bleeding episodes compared to UFH-treated patients. (13) This is an interesting finding when we consider that DVT prophylaxis with LMWH in various surgical populations has been associated with a greater incidence of bleeding than that observed with UFH. (18) The lower incidence of bleeding observed in trials involving medical patients may be related to the lower LMWH dose that was administered. After pooling LMWH surgical prophylaxis studies, a clear dose-response effect of LMWH related to bleeding risk has been demonstrated. (40) Patients appear to be at significantly greater risk for experiencing a bleeding episode when they receive more than 3400 anti-Xa IU of a LMWH per day. An additional safety advantage of using LMWH rather than UFH prophylaxis is the decreased incidence of heparin-induced thrombocytopenia observed with LMWH use. (17)

Low-molecular-weight heparin therapy can be administered on a once daily basis to patients and thereby will potentially decrease drug administration costs compared to the twice or thrice daily dosing regimens used with UFH. However, the significantly greater acquisition costs associated with LMWH therapy is unlikely to offset any administration-related savings. Although a formal pharmacoeconomic analysis of UFH versus LMWH prophylaxis in acutely ill medical patients has yet to be published, economic studies in other populations where UFH and LMWH therapeutic equivalence has been demonstrated (e.g. DVT prophylaxis in general surgery patients) have not revealed LMWH therapy to be cost-effective. (41)

Conclusion

Current literature demonstrates that acutely ill medical patients, (particularly those with respiratory failure or decompensated heart failure), without contraindications to therapy (e.g. active bleeding), should receive pharmacologic thromboprophylaxis. Substantial evidence now demonstrates that LMWH prophylaxis to be no more efficacious than UFH, except perhaps in patients with decompensated CHF. A decreased incidence of heparin-related adverse events (i.e. bleeding and thrombocytopenia) and the

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opportunity for once-daily dosing is certainly enticing, but is still unlikely to make LMWH a cost-effective alternative (over UFH) for DVT prophylaxis in acutely ill medical patients. Further LMWH versus UFH studies are needed in higher risk medical patients (e.g. mechanically ventilated MICU patients) to further delineate any advantages that this newer class of drugs may have in this population.

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Issues in Pharmacotherapy Practice

Pharmacological Management of Severe Traumatic Brain Injury: An Evidence-Based Review

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Abstract

Traumatic brain injury (TBI) accounts for almost one-half of all trauma fatalities and has a significant impact on mortality, morbidity, and health care costs. Understanding normal cerebral physiology and metabolic derangements due to primary and secondary injuries after TBI help to delineate cellular mechanisms of injury and identify potentially beneficial therapies. Neurological monitoring and adherence to objective, specific goals for initial resuscitation and support of the TBI patient are essential. Specific therapies such as cerebrospinal fluid drainage, diuretics, hyperventilation, barbiturates, and anticonvulsant prophylaxis have been studied. Many of these interventions have been empirically based on pathophysiologic rationale and have subsequently been implemented in the context of head-injury management protocols in an attempt to improve patient outcomes. Traditionally, studies evaluating TBI therapies have been limited by design flaws. However, larger better-designed trials have recently been undertaken, and meta-analytic techniques have also been employed to help establish the relative merit of various therapies for TBI. Unfortunately, early interest in many of these therapies has not translated into clinical benefits in well-designed trials. For these reasons, experimental therapies such as induced hypothermia, corticosteroids, indomethacin, and other neuroprotective strategies such as calcium channel blockers, antioxidants, 21-aminosteroids, antagonists of excitatory amino acids, cyclosporine, magnesium, and "Lund therapy" continue to be evaluated. The purpose of this review is to provide the reader with a comprehensive review of the pathophysiology, neurological monitoring, therapeutic goals, initial resuscitation strategies, and treatment options for the TBI patient.

J Inform Pharmacother 2000;3:309-335.

Introduction

Trauma results in about 150,000 deaths in the United States each year, and approximately one-half of this mortality is specifically related to head injuries. (1) The 1-year survival rate following a head injury is lower in patients over 50 years of age, possess lower initial Glasgow Coma Scores and higher Injury Severity Scores, lack pupillary responses, reveal a hematoma on CT scan, and in those who demonstrate evidence of brainstem injury. (2) Although mortality is the principal endpoint, the long-term functional outcome following a head injury is also crucial. Tragically, approximately 200,000 people in the U.S. live with disabilities caused by traumatic brain injuries. (1) The economic impact of these injuries is also substantial. The initial treatment cost per severe head injury is estimated to be approximately \$150,000 U.S. and a 1990 report estimates total direct and indirect lifetime costs to be \$158 billion U.S for all head injuries in the U.S. (3)

It is now generally recognized that secondary as well as primary injury contributes to the morbidity and mortality of traumatic brain injury (TBI). Brain swelling and increased intracranial pressure (ICP) promote secondary injury, and it has been hypothesized that intracranial hypertension may be the primary cause of death in some patients. (4,5) Aggressive management protocols, including ICP control, have been shown to reduce the overall mortality and morbidity rate. (1,6,7,8) According to data from the Traumatic Coma Data Bank (TCDB), such protocols have resulted in an overall mortality reduction following severe head injury from 50% to 36%. (9) Despite these encouraging results, several currently

applied therapies remain to be properly evaluated in well-designed trials and new pharmacological strategies to control ICP, improve cerebral oxygenation, and reduce morbidity and mortality are still needed to further improve patient outcomes.

The purpose of this review is to provide an overview of cerebral physiology under normal conditions and during TBI, provide an outline of monitoring strategies for TBI patients, review current treatment strategies to control ICP and optimize cerebral oxygenation in TBI patients, and discuss experimental therapies in the pharmacological management of TBI.

Normal Cerebral Physiology

Although the brain represents only 2% of total body weight, it utilizes 20% of the systemic oxygen consumption for the oxidation of glucose. (10,11) The metabolic rate of the brain is often expressed in terms of its rate of oxygen consumption (CMRO₂), which is approximately 3.5 mL/100g brain/min. (10,11) Approximately 15% of cardiac output is distributed to the brain (750 mL/min), and normal cerebral blood flow (CBF) in an adult remains relatively constant at 40-50 mL/100 g brain/min. (10,11) Under normal conditions, the brain has little energy reserve, so CBF is tightly coupled to CMRO₂ and brain function. As cerebral metabolism and oxygen consumption increase, metabolic autoregulation results in a parallel increase in CBF and cerebral oxygen delivery (CDO₂). (10) Cerebral blood flow is tightly regulated to metabolism in order to maintain oxygen supply in balance with oxygen demand, and to protect the brain from extremes in perfusion pressure due to hypertension. Cerebral blood flow autoregulation permits cerebral vasculature to alter cerebrovascular resistance (CVR) to maintain a constant CBF despite variations in cerebral perfusion pressure (CPP). Accordingly, CBF is equal to CPP/CVR. (10,12) Cerebral perfusion pressure is determined by the mean arterial pressure (MAP), and ICP, thus CPP is equal to (MAP - ICP). (10,12) Under normal conditions, despite variations in MAP (between 50 and 150 mm Hg) and concurrent variations in CPP, CBF remains relatively constant due to alterations in CVR. Mean arterial pressure below 50 mm Hg may result in cerebral ischemia, while MAP above 150 mm Hg may result in capillary injury or edema. (10,11,12)

Intracranial pressure is measured most reliably from within the ventricle and is normally less than 15 mm Hg. The skull is a rigid compartment containing brain tissue (80%) cerebrospinal fluid (CSF) (10%), and blood volume (10%). (13) The Monroe-Kellie doctrine states that these incompressible structures within the cranial vault are in a state of volume equilibrium, and any increase in the volume of one component must be compensated for by one or more of the other components to ensure that intracranial volume remains constant. (14,15) Any disturbances in intracranial volume will alter ICP, while any increase in ICP will reduce CPP and may reduce CBF if alteration in CVR via autoregulation is not functional. Factors that normally influence cerebral autoregulation include carbon dioxide and oxygen. As PaCO₂ drops to between 20-80 mm Hg, there is a linear decrease in CBF. (10,16) Hypocapnia decreases CBF and hypercapnia increases CBF. (10,11,16) In fact, CBF increases 2-3% per mm Hg increase in PaCO₂ above 40 mm Hg. (10,11,16) Hypoxemia also affects autoregulation, and when PaO₂ drops below 50 mm Hg, CBF doubles. (10,11,16) The extraction of oxygen from the cerebral blood (CEO₂) is defined as the difference between arterial oxygen saturation (SaO₂) and jugular venous oxygen saturation (SjvO₂), thus CEO₂ is equal to SaO₂-SjvO₂. (17) Under normal conditions, SjvO₂ is 55-71%, and CEO₂ is relatively constant at 24-42%. (17) The cerebral extraction ratio (CERO₂) is defined as the ratio between cerebral oxygen consumption (CMRO₂) and cerebral oxygen delivery (CDO₂), CMRO₂/CDO₂. CERO₂ is practically expressed as (SaO₂-SjvO₂)/SaO₂. Normal CERO₂ is around 35% ± 10%. Major causes of decreases in SjvO₂ and thus increases in CERO₂ can be due to reduced cerebral oxygen delivery (CDO₂) or increased cerebral oxygen consumption (CMRO₂). The normal cerebral physiology can be summarized by the equations in [Table 1](#).

Table 1. Normal Cerebral Physiology

Equations	Definitions

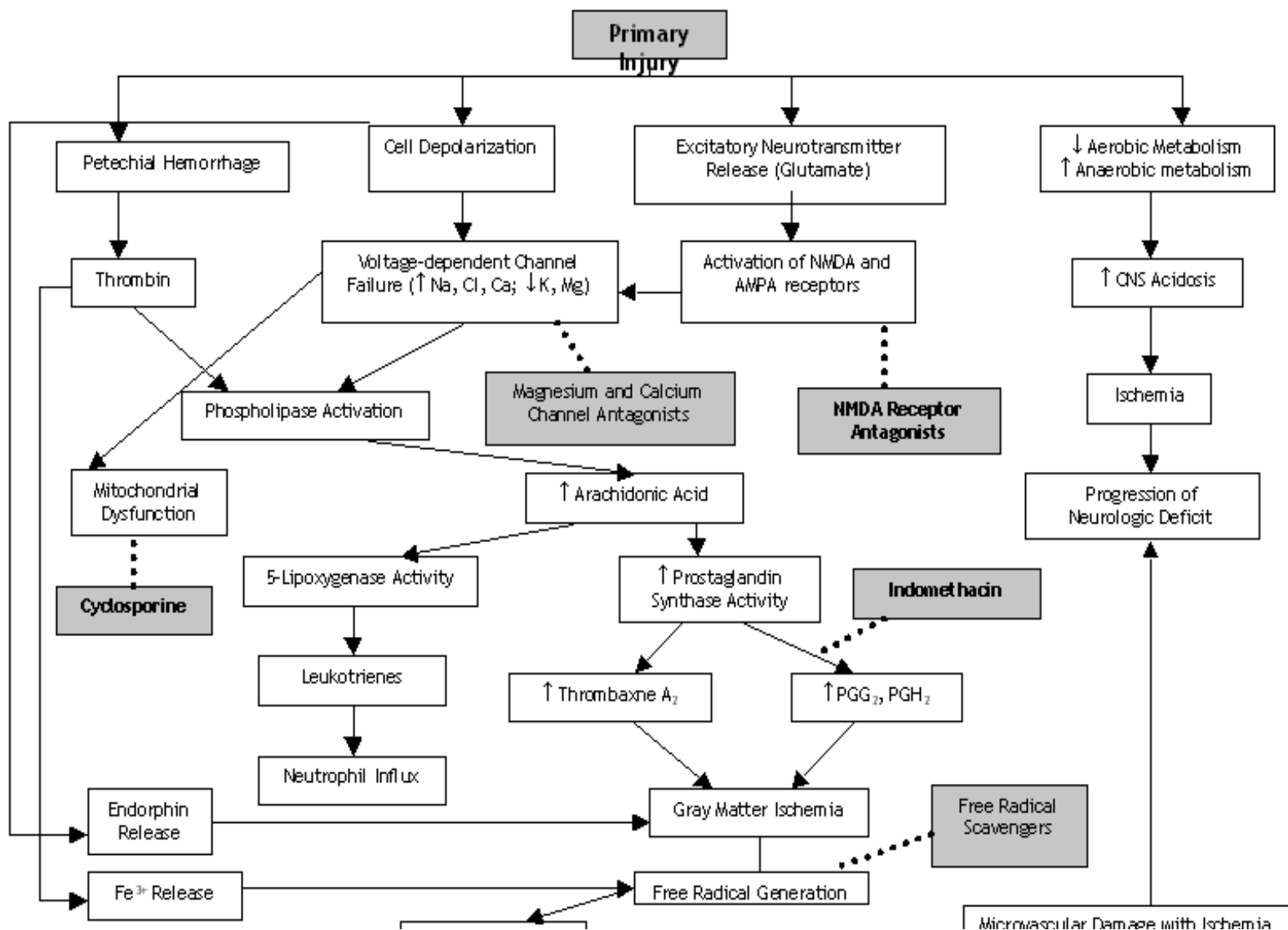
$CBF = CPP / CVR$
 $CPP = MAP - ICP$
 $CBF = (MAP - ICP) / CVR$
 $CEO_2 = SaO_2 - SjvO_2$
 $CERO_2 = CMRO_2 / CDO_2$
 $CERO_2 = (SaO_2 - SjvO_2) / SaO_2$

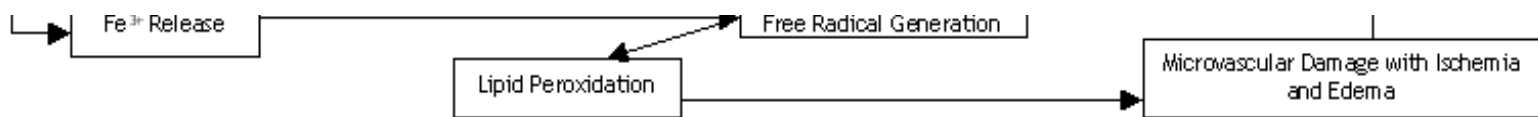
CBF: Cerebral blood flow
 CPP: Cerebral perfusion pressure
 CVR: Cerebral vascular resistance
 MAP: Mean arterial pressure
 ICP: Intracranial pressure
 CBF: Cerebral blood flow
 CEO₂: Cerebral oxygen extraction
 SaO₂: Arterial oxygen saturation
 SjvO₂: Jugular venous oxygen saturation
 CERO₂: Cerebral extraction ratio of oxygen
 CMRO₂: Cerebral metabolic consumption of oxygen
 CDO₂: Cerebral oxygen delivery

Pathophysiology of TBI

Neurological complications from TBI can occur as a direct result of the primary injury, or may be caused by secondary injuries that follow within minutes to days. The primary injury is typically the result of a direct initial insult and the secondary injury is caused by the subsequent cascade of biochemical changes that are triggered by ischemia and result in a disruption of the normal central nervous system balance between oxygen supply and demand (Figure 1).

Figure 1. Illustration of Secondary Neurologic Injury Cascade with the Potential Role of Indomethacin and Neuroprotective Agents





Following ischemia, cells release the excitatory amino acid glutamate and adenosine triphosphate (ATP) levels will decrease. Glutamate activates N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), kainate, and metabotropic receptors. (16,18) Activation of these receptors results in a failure of the cellular ionic pump with rapid influxes of calcium and sodium into the cell and subsequent depolarization. Calcium has several deleterious effects including cerebral vasospasm, mitochondrial dysfunction, and activation of proteases and lipases. The effect of lipase stimulation is the formation of several arachidonic acid derivatives including thromboxane A₂ (TXA₂), prostacyclin (PGI₂), prostaglandin G₂, prostaglandin H₂ and leukotrienes. (16,18) The resulting effects of these arachidonic acid derivatives are platelet aggregation, vasodilation and oxygen free radical production with lipid peroxidation. Decreased ATP levels leads to a diminished ion gradient with increases in lactate and subsequent acidosis and ischemia. (18) The entire secondary injury process is a vicious cascade of biochemical changes that leads to further spread of the ischemic injury and neurological deficits. The causes of secondary injury include cerebral edema, expanding mass lesions, and cerebral vasospasm. (12) Other factors that may potentiate secondary injury include elevated temperature, seizures, and agitation. (12) The loss of cellular integrity from the ionic shifts may result in cytotoxic edema and vasogenic edema may also develop due to cerebral capillary endothelial damage. (12)

The swelling of injured tissue after TBI tends to peak within 72 hours of injury and leads to cerebral edema. The most detrimental consequence of this cerebral edema is increased ICP since it leads to significant morbidity and mortality. (1,4,5,6,7,8,10) If the CSF or cerebral blood volume cannot be reduced to compensate for the increased brain volume, the ICP will rise. The less compliant the brain is, the higher the ICP will rise for a given amount of cerebral edema. Raised ICP compresses brain tissue and decreases CPP, further increasing cerebral injury. (12) Cerebral injury affects autoregulation, which would normally help combat changes in pressure associated with neurological injury. (12) Autoregulation can be either impaired, or preserved at lower levels of CBF after TBI. Thus, the injured brain may be especially susceptible to hypotension that reduces CPP and causes cerebral ischemia in the early post-injury phase.

Cerebral metabolic consumption of oxygen is globally depressed in severely head-injured patients with systemic energy expenditure decreasing from 20% to 11% (10). The reduction in CMRO₂ is proportional to the severity of coma, as reflected by the Glasgow Coma Scale (GCS). (Table 2) (19,20)

Table 2. Glasgow Coma Scale

Neurologic Function	Response	Score
Eye Opening (/4)	Spontaneous	4
	To sound	3
	To pain	2
	No response	1
Best Motor Response (/6)	Obeys commands	6
	Localizes pain	5
	Flexion (withdraws)	4
	Abnormal flexion (decorticate rigidity)	3
	Abnormal extension (decerebrate rigidity)	2
	No response	1
Best verbal response (/5)	Oriented	5

Confused conversation	4
Inappropriate words	3
Incomprehensible sounds	2
No response	1

TOTAL (/15)	(3-15)

There are three scenarios describing cerebral oxygenation during the period of reduced CMRO₂. (Table 3) In approximately 45% of patients, there is normal coupling between the CMRO₂ and CBF. (10,11) Decreased neuronal metabolism and CO₂ production leads to a reduction in CBF that is proportional to the reduced CMRO₂ while the CERO₂ remains unchanged. (17) In this scenario, there is intact metabolic autoregulation and a balance between cerebral oxygen consumption and delivery. The second scenario is termed "oligemic cerebral hypoxia" or "misery perfusion". Coupling between CMRO₂ and CBF is lost, and CBF is low relative to the needs of the brain. If cerebral oxygen delivery is reduced due to hypotension, systemic anemia, systemic hypoxemia, high ICP, cerebral vasospasm, or marked hypocapnia, the brain responds by increasing the extraction of oxygen to compensate, the S_{ij}VO₂ will fall and the CERO₂ will increase. (10,17) However, a point will be reached at which further decreases in CBF cannot be compensated for by increased oxygen extraction and ischemia follows, manifested by a CERO₂ above 40%. (17)

Table 3. Cerebral Oxygenation Alterations After TBI

Scenario	CMRO ₂	CBF	CERO ₂	Comment
Intact metabolic autoregulation	↓	↓	↔	Normal coupling and extraction
Oligemic cerebral hypoxia (misery perfusion)	↓	↓↓	↑	Cerebral ischemia may cause secondary injury
Relative cerebral hyperperfusion (luxury perfusion)	↓	↑	↓	Excess CBV may increase ICP and cause secondary injury

CMRO₂ = Cerebral metabolic consumption of oxygen, CBF = Cerebral blood flow, CERO₂ = Cerebral extraction ratio of oxygen, CBV = Cerebral blood volume, ICP = Intracranial pressure

Within 6 hours of injury, there is a global reduction in CBF to ischemic levels in 13% of patients. (21) If there is a severe reduction of CBF for a sufficient duration of time, these ischemic changes will become irreversible and lead to brain tissue infarction. Increases in cerebral oxygen delivery after this point will not result in greater CEO₂ because of permanent tissue damage. Under these conditions, the S_{ij}VO₂ will actually increase and the CERO₂ will fall, indicating permanent damage. (10) To prevent cerebral ischemia, treatment strategies must focus on increasing cerebral oxygen delivery (CDO₂) or reducing oxygen consumption (CMRO₂). Major causes of reduced CDO₂ include systemic hypotension, increased ICP and thus low CPP, systemic anemia, systemic hypoxemia, cerebral vasospasm, or marked hypocapnia. (10) Major causes of increased CMRO₂ include agitation (e.g. pain, anxiety, or delirium), fever, and seizures. (10)

The final scenario is that called "relative cerebral hyperperfusion" or "luxury perfusion". Coupling between CMRO₂ and CBF is lost, and CBF is excessive to that required to meet the metabolic needs of the brain. (17) This increase in cerebral blood volume may contribute to a high ICP thus reductions in cerebral blood volume or overall ICP are indicated. In this scenario, the S_{ij}VO₂ is high, and the CERO₂ remains low. (17)

Neurological Monitoring in TBI Patients

Neurological monitoring in TBI patients may include physical and neurological examinations, ICP monitoring, S_{ij}VO₂ monitoring, electroencephalographic (EEG) monitoring, and transcranial doppler (TCD) ultrasonography. (22,23) A

complete physical and neurological examination including brainstem function, GCS, and cranial nerve function are indicated to establish the extent of the injury, and to establish a baseline for neurological monitoring. (22,23) The GCS is used to evaluate the level of consciousness according to eye opening, best motor response, and best verbal response. The admission or last known GCS is used to grade the severity of TBI. A GCS score of 13-14 indicates mild injury, a score of 9-12 indicates moderate injury, while a score of 3-8 indicates severe injury. (24) The GCS has also been shown to be a useful predictor of one-year survival and cognitive recovery. (2,24)

Although outcome benefits of ICP monitoring have never been assessed in a prospective, randomized clinical trial, it is nevertheless considered essential for the patient with severe TBI. (1) Increases in ICP have been associated with worse neurological outcomes, (5,25,26,27,28) and it has been suggested that intracranial hypertension is the primary reason for death in some patients. (4,5) Moreover, the use of intensive ICP-based management protocols have been associated with significant reductions in morbidity and mortality from TBI. (5,6,7,8,9,29) In one prospective, randomized controlled trial, mortality was shown to be significantly lower in patients for whom ICP was successfully controlled with barbiturate therapy. (29) However, there have been no prospective, randomized trials to compare outcomes using different treatment thresholds for ICP. (1) The investigators of a small, uncontrolled non-randomized trial reported an associated reduction in mortality in patients whose ICP treatment was initiated at 15 mm Hg versus treatment initiated at 20-25 mm Hg. (6) Uncontrolled co-interventions and potential biases in the trial design may explain these results. Another recently published study involved an examination of the relationship between ICP, CPP and outcome. (30) Juul et al. reviewed these parameters in a series of 427 patients who were enrolled in the randomized, double-blind trial of Selfotel, a NMDA receptor antagonist. They reported that treatment protocols should emphasize immediate treatment of ICP greater than 20 mm Hg and that CPP greater than 60 mm Hg had very little influence on patient outcome. (1) The likelihood of herniation due to high ICP may also depend on the location of the intracranial mass lesion. (1,11,31) For example, lesions of the anterior temporal lobe can cause herniation at an ICP level of less than 15 mm Hg. (31) The Brain Trauma Foundation (BTF) guidelines contain recommendations for continuous ICP monitor placement in patients with a GCS of 8 or less with an abnormal admission CT scan, or in high-risk (age greater than 40 years, motor posturing, or systolic blood pressure under 90 mm Hg) severe head injury patients with a normal CT scan. Ventricular catheters connected to an external strain gauge are considered to be the most accurate, least costly, and most reliable method for monitoring ICP. The use of these catheters also allows for the therapeutic drainage of CSF. (1) The BTF and European Brain Injury Consortium (EBIC) Guidelines recommend 20-25 mm Hg as the upper threshold at which treatment to lower ICP should be initiated. (1,32) In summary, ICP monitoring helps determine prognosis, enables early detection of mass lesions, allows monitoring of interventions to lower ICP, enables CSF drainage to reduce ICP, and enables calculation and optimization of CPP.

Cerebral ischemia may be the single most important secondary event influencing outcome following severe TBI. (33) CPP is the physiologic variable driving CBF and energy delivery, and therefore it is closely related to ischemia. Reducing elevated ICP or artificially increasing the MAP can increase CPP. While there have been concerns that strategies to increase MAP to achieve a higher CPP may increase brain swelling and raise ICP, studies by Bouma and Bruce have shown that BP increases of as much as 30 mm Hg does not significantly alter ICP. (34,35) This phenomenon appears to exist regardless of whether or not patients had intact cerebral autoregulation. No prospective, randomized, controlled studies have definitively proven that intracranial hypertension, morbidity or mortality is reduced by maintaining CPP values at or above 70 mm Hg. (1) However, CPP has been shown to be strongly correlated to mortality, (36) and several investigators have also demonstrated an associated decrease in patient morbidity and mortality when CPP is actively sustained above 70 mm Hg. (37,38,39,40,41) One study involving 189 patients compared the effects of a CBF-targeted protocol that kept CPP over 70 mm Hg and PaCO₂ at 35 mm Hg, versus an ICP-targeted protocol that kept CPP above 50 mm Hg and PaCO₂ at 25-30 mm Hg. (42) The CBF-targeted protocol reduced the frequency of jugular desaturation from 50.6% to 30% (p=0.006). (42) This study was not powered to determine a difference in neurological outcome. (42) These preliminary data suggests that a CPP of at or above 70 mm Hg may reduce both global and regional ischemia and limit secondary injury. Therefore, the BTF and EBIC Guidelines suggest that CPP be maintained above 70 mm Hg. (1,32)

There is no practical method for measuring CMRO₂ or CBF in the ICU setting. Although jugular venous saturation monitoring does not give quantitative information about either CMRO₂ or CBF, it reflects the ratio between these two variables. By utilizing SaO₂ and SjvO₂, the CEO₂ and CERO₂ can be calculated (Table 1), and the balance between CMRO₂ and CDO₂ can be determined (Table 2). In this way, it is possible to know if CMRO₂ and CBF are appropriately coupled, or if the injured brain is undergoing "oligemic cerebral hypoxia" or "luxury perfusion". The occurrence of one episode of jugular venous desaturation was associated with a two-fold increase in the risk of poor neurological outcome while multiple episodes were associated with a 14-fold increase in risk. (43) Monitoring of SjvO₂ is useful because ICP and CPP are pressure monitoring strategies and may not detect cerebral ischemia. (44) Therefore some have advocated using jugular venous bulb saturation monitoring to optimize cerebral oxygenation. (44,45) It may also be especially useful in situations where ICP monitoring is not readily available or coagulation abnormalities contraindicate the use of ICP monitoring. (44,45) One prospective interventional study involved a comparative outcome assessment of 353 patients with severe acute brain trauma who underwent both management of cerebral extraction of oxygen and cerebral perfusion pressure versus patients who underwent monitoring and management of cerebral perfusion pressure alone. At 6 months

post injury, patient outcomes were significantly better in the group who underwent cerebral extraction of oxygen monitoring. (17) Monitoring of $SjvO_2$ is considered to be very useful for monitoring therapies used in TBI patients. Therapeutic strategies such as hyperventilation and indomethacin may reduce ICP at the expense of inducing cerebral ischemia, and worsening secondary brain injury and neurological outcome (46,47). These acute therapies can be safely monitored using a jugular bulb saturation monitor that will detect a drop in $SjvO_2$ and increased $CERO_2$ indicating cerebral ischemia. Drawbacks of jugular bulb catheter monitoring include the potential for complications, and the cost of the catheters themselves. There are technical difficulties associated with catheter placement, and anatomical structures close to the internal jugular vein can be injured during catheterization. (45) Once placed, the position of the catheter tip within the jugular bulb should be confirmed radiographically. (45) Complications of $SjvO_2$ monitoring are rare, with a 4.5% incidence of carotid artery puncture, and 40% incidence of subclinical jugular thrombi. (48) In summary, jugular bulb monitoring is used to optimize cerebral oxygenation by providing information on $CERO_2$, and ensuring normal coupling between $CMRO_2$ and CBF during management of TBI. The BTF Guidelines acknowledge that jugular venous oxygen saturation monitoring may be useful by identifying cerebral ischemia induced by therapies such as hyperventilation. (1)

Electroencephalogram tracings closely correlate with $CMRO_2$. (10) In normal adults, infusion of barbiturates until the EEG becomes flat reduces the $CMRO_2$ by 50% to an average of 1.5 mL/100g brain/min. (49) Therefore it is useful in sedative titration in barbiturate coma. The EEG is also considered to be the best method for detecting seizure activity, and is especially useful in patients on paralytic agents or those suspected of having non-convulsive status epilepticus. (50) Vespa et al. recently reported their observations with the incidence and impact of nonconvulsive and convulsive seizures in a series of 94 moderate to severe TBI patients. (51) Overall, convulsive and nonconvulsive seizures occurred in 21 patients (22%), with 6 cases of status epilepticus. (51) All patients with status epilepticus died, compared with a mortality rate of 24% in the group without seizures ($p < 0.001$). (51) In more than half of the cases, the seizures were nonconvulsive and were diagnosed solely by EEG. (51) Moreover, the mean serum phenytoin blood concentration in patients with seizures was 66.4 $\mu\text{mol/L}$, which is considered to be within the usual therapeutic range for phenytoin. Thus, it can be seen that there is a significant occurrence of nonconvulsive seizures in TBI patients, and that these seizures may occur in the presence of appropriately dosed prophylactic phenytoin therapy. Although there is a valuable role for continuous EEG monitoring in the TBI patient, continuous EEG monitoring is not routinely used in all centers.

Transcranial Doppler (TCD) ultrasonography measures cerebral blood flow velocity, which is a surrogate marker of CBF. (52) When flow through a vessel is constant, cerebral blood flow velocity increases inversely to the vessel's cross-sectional area. (52) Analysis of TCD waveform and blood flow velocity can indirectly provide information about CBF and ICP. The analysis of the velocities during the cardiac cycle is presented as a waveform. Current machines calculate a mean flow velocity and the pulsatility index (PI). The PI (equal to $[\text{systolic velocity} - \text{diastolic velocity}] / \text{mean velocity}$) is an index of vascular resistance. Therefore, this index would be elevated in patients with increased ICP. Vasospasm is defined as a mean flow velocity above 102 cm/sec. Transcranial doppler monitoring can be used to detect vasospasm, assess blood flow patterns, determine patency of cerebral vessels, and detect elevated ICP in TBI patients. (53) The most important limitation of TCD monitoring is the technical ability of the neurologist. (52) In summary, TCD is a non-invasive method that may be used to assess the adequacy of cerebral blood flow in an attempt to differentiate hyperemia from vasospasm and to assess the status of cerebral autoregulation in TBI patients. (52)

Goals of Therapy for TBI

The overall goals of management for TBI patients are to reduce mortality, morbidity, and improve long-term functional outcome. Secondary brain injury can be prevented and/or limited by optimizing cerebral resuscitation. Specific goals of therapy published in existing TBI guidelines and consensus papers include: 1) controlling ICP to less than 20-25 mm Hg (1); 2) maintaining CPP at or greater than 70 mm Hg or MAP above 90 mm Hg if an ICP monitor is not in place; 3) optimizing cerebral oxygenation by ensuring normal coupling between $CMRO_2$ and CBF and maintaining CEO_2 above 42% ($CERO_2$ above 40%); and 4) preventing and/or treating cerebral and systemic complications of TBI. (1,32)

Therapeutic Interventions for TBI

Initial Resuscitation

As with any trauma patient, the initial priorities are establishment of an adequate airway, breathing, and circulation. If the patient's level of consciousness is impaired to the extent that the airway cannot be protected, intubation is required. (22,23,54) Mechanical ventilation may be indicated in the setting of hypercapnic or hypoxemic respiratory failure caused by a decreased level of consciousness, atelectasis, pneumothorax, or pulmonary edema. Mechanical ventilation may enable brief hyperventilation that may be indicated for acute increases in ICP. Oxygen saturation should be maintained above 90 % and paO_2 above 60 mm Hg. (1,32,54)

Circulating volume must also be restored with packed red blood cells if the hematocrit is less than 30%, and isotonic (0.9%) saline for further fluid resuscitation. (22,23) Colloids (mannitol and albumin) and hypertonic saline (3% and 7.5%) have been studied for initial resuscitation; however data from prospective trials have not shown clinically significant advantages in resuscitation or neurological outcome. (55,56,57,58,59) Hypotonic fluids should not be used for initial fluid resuscitation, as they may lead to hyponatremia and a hypo-osmolar state that may exacerbate cerebral edema. The goal of fluid resuscitation and fluid maintenance should be euvolemia without reducing plasma osmolarity. (22,23,54) If fluids alone do not restore MAP to 90 mm Hg, inotropic and vasopressor agents such as dopamine, phenylephrine, and norepinephrine may be required. (54)

Adequate resuscitation is vital as SBP less than 90 mm Hg or hypoxia (apnea or cyanosis in the field or a PaO₂ less than 60 mm Hg) are strong independent risk factors for mortality, and worse neurological outcome. (25,58,60,61,62) Once initial resuscitation measures have been completed, diagnostic evaluation with a CT scan is indicated, along with a complete physical and neurological exam, serum chemistry, hematology, and toxicology screening. (22,23,32,54)

General Supportive Measures

Once the TBI patient is stabilized and diagnostic tests have been completed, several routine, general supportive measures should be undertaken.

Central venous catheters, arterial catheters, jugular venous bulb catheter, and an ICP monitoring device should be placed, if indicated. (1,22,23,53) The head of the bed should be elevated to 30 degrees with the patients head stabilized in a neutral position to enable adequate venous drainage and prevent venous outflow obstruction that may increase ICP. (1) Maintenance fluids should be isotonic saline, and the serum sodium and plasma osmolarity should be maintained within the normal range. Euvolemia should continue to be the goal fluid status. Fluid therapy should be utilized to help maintain an adequate MAP above 90 mm Hg if an ICP monitor is not in place, or to a CPP > 70 mm Hg utilizing an ICP monitor. (1,32) If the MAP is low, and the CVP or pulmonary capillary wedge pressure (PCWP) is adequate, vasopressors may be required to increase MAP above 90 mm Hg or to achieve a CPP of 70 mm Hg or greater. (1,32,54)

Serum glucose should be maintained at 4-7 mmol/L as data suggests that hyperglycemia in the setting of ischemia may worsen outcome. Two retrospective reviews have attempted to describe the effect of hyperglycemia on outcome in TBI patients. (63,64) Margulies et al. found that peak glucose levels were inversely related to both GCS on admission and GCS at discharge ($p < 0.001$) in 97 patients with intracranial injuries. (63) However these peak glucose levels may simply reflect the severity of illness and injury in this population as peak glucose was not an independent predictor of outcome in this series. (63) Lam et al. retrospectively reviewed the relationship between serum glucose and outcome in 169 head-injured patients. (64) Patients with lower GCS scores had higher serum glucose concentrations, and patients who remained in a persistent vegetative state or died had significantly higher glucose concentrations than those patients with a good outcome or moderate disability. (64) In the severely injured subgroup (i.e. GCS less than 8), a serum glucose of greater than 11.1 mmol/L was associated with a significantly worse outcome ($p < 0.01$). (64) For these reasons, prevention of hyperglycemia and aggressive control of elevated blood glucose is required. Intravenous fluids (including medication piggybacks) should not contain dextrose, frequent blood glucose monitoring with a glucometer should be performed, and sliding scale insulin may be required to control blood glucose levels.

Oxygen saturation should be maintained above 90% and the PaO₂ should be kept at 60 mm Hg or greater. (1,32,54) Positive end expiratory pressure and inverse ratio ventilation may be required in patients with a pulmonary shunt or oxygenation difficulties, and these modalities may be used safely in TBI patients without compromising ICP. (65,66)

Fever is common in head-injured patients, and increases the body's metabolic rate by 10-13% per degree Celsius. (67,68) Patients with hyperthermia have been shown to have worse neurological outcomes than those patients who remain normothermic. (43) Measurement of rectal temperature alone may significantly underestimate brain tissue temperature by 0.5-2.0°C. (67,68,69) For these reasons, fever prophylaxis with acetaminophen 650 mg every four hours and/or a cooling blanket should be used to maintain at least normothermia, and possibly hypothermia.

Pain, anxiety, and delirium manifested as agitation along with coughing, respiratory suctioning, and ventilator asynchrony can cause increases in cerebral oxygen consumption and ICP. (10) Thus opioid analgesics, sedatives, and neuromuscular blocking agents may be required. There have been no large studies comparing the effects of sedative agents on outcome in patients with severe head injury. (1,70) Thus, the use of analgesic, and sedative agents should be titrated based on cerebral hemodynamic and oxygenation goals (ICP, CPP, and CERO₂) or by using sedation scales validated in critically-ill patients. (71,72,73) Although opioids have been associated with increases in ICP, several studies have refuted this effect, even with newer, synthetic opioids. (74,75) Until definitive evidence is available, opioids may be used in TBI patients, and ICP should be followed for possible drug-related increases. Tipps et al. recently reported a small case series in which the

newer synthetic opioid, remifentanyl was evaluated in the neurological intensive care unit. (76) These investigators found that the ultra-short duration of action of remifentanyl facilitated frequent neurological examinations and no patient experienced deleterious hemodynamic or neurological effects from the use of this drug. (76) Propofol is a sedative-hypnotic agent formulated in a 1% solution in a 10% intralipid carrier. Propofol causes dose-dependent decreases in CMRO₂, CBF, ICP, MAP, and CPP. (77) The advantage of this drug is that it can be titrated easily and patients can be awoken quickly to enable neurological evaluation; however, it does not possess any analgesic properties. A recent pilot, prospective, randomized, double-blind trial compared morphine alone to morphine plus propofol in 42 patients with severe head injury. (77) The use of neuromuscular blocking agents, benzodiazepines, pentobarbital, and CSF drainage was less in the propofol group, and the use of vasopressors was higher in the propofol group due to hypotension. (77) Mortality and neurological outcome was no different between the groups. (77) Until there has been a clinically significant advantage proven with propofol, other sedative agents can be used. If propofol is used, MAP should be monitored closely to ensure CPP is not compromised. Neuromuscular blocking agents may be required in TBI patients; however, they should not be routinely used. A prospective, randomized trial of 514 severely head injured patients examining the effects of prophylactic neuromuscular blockade showed that the intervention group had a longer intensive care unit stay, a higher incidence of pneumonia, and a trend toward more frequent sepsis. (78) Complications of neuromuscular blockade including prolonged paralysis and prolonged weakness mandate that these agents be reserved. General measures are used along with specific therapeutic modalities to keep ICP less than 20 mm Hg, maintain CPP at 70 mm Hg or greater, and CERO₂ below 40%.

Specific Treatment Modalities

Various specific therapeutic modalities studied in the management of TBI patients have focused on preventing or treating increases in ICP by reducing cerebral blood volume, CSF volume, or brain volume as per the Monroe-Kellie doctrine. (14,15) Lowering ICP or raising MAP will increase CPP. Other therapies have focused on reducing CMRO₂ or increasing CDO₂ to improve cerebral oxygenation and maintain CERO₂ below 40%. Specific therapies include CSF drainage, hyperventilation, mannitol, barbiturate-induced coma, and seizure prophylaxis.

CSF Drainage

The BTF Guidelines recommend ventricular catheters as the ICP monitoring method of choice because of their accuracy, ability to be recalibrated, and because of their ability to drain CSF to acutely lower ICP. (1) Although CSF drainage is recommended as one of the first methods to acutely lower ICP, its effectiveness has never been studied in a randomized clinical trial. (79)

Diuretics

Mannitol has been used to treat suspected or proven increases in ICP in TBI patients. The BTF Guidelines state that the benefits of this drug are assumed to be related to an immediate plasma-expanding effect that reduces the hematocrit, reduces blood viscosity, increases cerebral blood flow, and increases CDO₂. This may explain why mannitol reduces ICP within minutes, and why its effects appear more pronounced in patients with low CPP (less than 70 mm Hg). Secondly, mannitol is thought to establish an osmotic gradient between plasma and brain cells and reducing cerebral edema and ICP by drawing water across an intact blood-brain barrier from the brain into the vascular compartment. (1,12)

Mannitol can be administered at 0.25-1.0 g/kg IV q4h, with an onset of action of several minutes, a peak effect between 20-40 minutes and a variable duration of action. (80) Mannitol administration has been associated with several neurological and systemic adverse effects. Mannitol can worsen vasogenic cerebral edema by passing across an opened blood-brain barrier and causing a reverse osmotic shift to draw water into brain cells, worsen cerebral edema, and paradoxically increase ICP. (81) Although there are no published randomized controlled trials that have compared different modes of administration (bolus versus infusion) or different doses, preliminary data suggests that the accumulation of mannitol in the brain is most marked when mannitol is in circulation for long periods, as occurs with continuous infusions. (1) Other potential adverse effects associated with mannitol administration may be acute congestive heart failure and pulmonary edema, hyperosmolar dehydration and hypotension with prolonged administration, hyponatremia, hypokalemia, acute renal failure when serum osmolality exceeds 320 mOsm/kg, and potential rebound increases in ICP after discontinuation of prolonged therapy. (80)

The effect of mannitol on neurological outcome and mortality has been studied in three well-designed randomized controlled trials, and has been subjected to meta-analysis. A prospective, randomized, double-blind trial by Sayre et al. compared pre-hospital administration of 5 mL/kg of 20% mannitol over 5 minutes compared to 5 mL/kg of normal saline in 41 patients with moderate to severe head injuries. (82) No data were provided for ICP, or disability, but relative risk (RR) for death at 2 hours was 1.75 (95% CI 0.48 - 6.38). (82) This study failed to show a benefit from mannitol, and also failed

to exclude a harmful effect on outcome. (82) Smith et al. conducted a prospective, randomized, double-blind trial comparing the administration of ICP-directed and empiric mannitol therapy in 77 patients with severe head injuries. (83) This study also failed to show a benefit of mannitol therapy with a RR of death at one year of 0.83 (95% CI 0.47-1.46). (83) Schwartz et al. conducted a prospective, randomized, single-blind trial comparing 1 g/kg of 20% mannitol plus additional boluses versus a load and continuous infusion of pentobarbital in 59 patients with severe head injuries and raised ICP for less than 15 minutes. (84) Again, this trial failed to show a beneficial effect of mannitol on outcome with a RR of death of 0.85 (95% CI 0.52-1.38). (84)

A Cochrane Collaboration meta analysis confirmed that there are insufficient data to preclude either a harmful or beneficial effect of mannitol on mortality. (85) Thus, despite acute reductions in ICP and improvements in CBF, mannitol has not been shown to improve neurological outcome or reduce mortality. Thus the therapeutic goals of therapy for mannitol should be to optimize control of ICP, CPP, and CERO₂. The BTF Guidelines recommend mannitol for treatment of elevated ICP in bolus doses of 0.25-1.0 g/kg body weight. (1) Mannitol can be administered to patients without ICP monitoring if there are signs of transtentorial herniation or progressive neurological deterioration not attributable to systemic pathology. (1) Serum osmolality should be kept below 320 mOsm/kg and adequate fluid replacement should be given to maintain euolemia. (1)

Furosemide is a loop diuretic that has also been shown to be effective in reducing ICP, but to a lesser extent than mannitol. (86) Unlike mannitol, furosemide will decrease production of CSF. (87) When used in combination with mannitol, furosemide (0.1-1 mg/kg) enhances the degree and duration of ICP reduction and it decreases the risk of rebound ICP elevation. (88) A concern associated with the routine use of furosemide is the potential of inducing massive diuresis that would result in depletion of the intravascular volume and electrolytes. Therefore this agent should be reserved to those patients who do not have a satisfactory response to mannitol.

Hyperventilation

Hyperventilation (HV) has been widely used in the treatment and prevention of raised ICP following TBI because it is simple, and rapidly reduces ICP. (1) Two recent surveys published in 1995 and 1996 respectively have shown that HV was used in 83% of American Centres, and 100% of United Kingdom Centres. (89,90) A recently published survey of American Centre neurosurgeons suggests that the use of prophylactic HV has dropped from 83% in 1991 to 36% in 1997. (91) The use of HV may be dropping due to concerns highlighted in the BTF Guidelines that outline potential drawbacks of HV and summarize the results of several clinical trials re-examining HV therapy. (1) Hyperventilation reduces ICP by causing cerebral vasoconstriction, with a subsequent reduction in CBF and CBV. (1) A potential drawback of HV is that although it may successfully control ICP, it may reduce CBF to ischemic levels. This can be seen during jugular venous bulb monitoring as a drop in SjvO₂, and rise in CERO₂. (10) Under conditions of "luxury perfusion" short-term HV could control acute increases in ICP, without adversely affected cerebral oxygenation. However, in situations of early brain injury (less than 6 hours) during "oligemic cerebral hypoxemia" when CBF is already uncoupled and insufficient to meet CMRO₂, further reductions induced by HV would be expected to further reduce CBF, induce cerebral ischemia, and potentially worsen secondary injury. (10,17,47) For these reasons, the practice of HV is under reassessment.

Muizelaar et al. performed a prospective, randomized, unblinded trial comparing normocapnia, HV, and HV plus tromethamine (THAM) buffering over 5 days in 77 patients with severe TBI and assessed neurological outcome at 3, 6, and 12 months. (46) Overall, the study failed to show a benefit of HV or HV plus THAM on combined death or severe disability (RR = 1.14 (95% CI 0.82-1.58), RR = 0.87 (95% CI 0.58-1.28)) or mortality (RR = 0.73 (95% CI 0.36-1.49), RR = 0.89 (95% CI 0.47-1.72)) respectively. (46) Interestingly, in the subgroup with a motor GCS score of 4-5, fewer patients had a favorable outcome (good or moderately disabled) in the HV groups at 3 and 6 months (p<0.05). (46) This difference did not remain significant after 12 months, likely due to a lack of statistical power. (1,46) Based on the results of this trial, the BTF has re-evaluated the practice of HV therapy. (1) The current BTF Guidelines recommend that in the absence of increased ICP, chronic prolonged HV therapy (PaCO₂ less than 25 mm Hg) should be avoided after severe TBI. (1) The use of prophylactic HV therapy (PaCO₂ less than 35 mm Hg) during the first 24 hours after severe TBI should be avoided because it can compromise CPP when CBF is reduced. (1) HV therapy is most appropriately reserved for acute neurological deterioration associated with elevated ICP, or for more prolonged periods when elevated ICP is refractory to other treatments. (1) The guidelines recommend that jugular venous saturation monitoring be used to monitor for cerebral ischemia if short-term HV resulting in a PaCO₂ of less than 30 mm Hg is required to acutely reduce elevated ICP. (1)

A recent study has been published that involved an evaluation of the effects of early moderate (PaCO₂ of 30 ± 2 mm Hg) hyperventilation in nine patients within 12 hours of injury. (92) In this study the investigators measured CBF, CMRO₂, CBV, cerebral venous oxygen content (CvO₂), and CERO₂. These investigators found that during hyperventilation, global CBF decreased, CBV fell, CERO₂ rose, CvO₂ fell, and CMRO₂ remained changed. They concluded that brief, moderate hyperventilation soon after injury does not alter cerebral metabolism and is unlikely to harm the patient. However,

further study is necessary to evaluate focal changes and the effects in patients with elevated ICP. (92)

Barbiturates

If CSF drainage, mannitol, and HV fail to control an elevated ICP and improve cerebral oxygenation, high-dose barbiturate therapy has been used as a last pharmacologic resort prior to emergency non-dominant temporal lobectomy with or without craniectomy. (1,22,23) Others have used barbiturate therapy prophylactically in an attempt to improve outcome. Barbiturates reduce CMRO₂, thus reducing cerebral metabolic demands, CBF, CBV, and ultimately ICP to enhance global cerebral perfusion and improve cerebral oxygenation. (1,93) At least one trial suggests that normal metabolic coupling between CMRO₂ and CBF is necessary for barbiturates to be effective. (94) Barbiturate therapy has also been associated with important complications such as infection, hypothermia, and hypotension (which may reduce CPP and offset any beneficial effects from ICP reduction). (93) Despite these controversies, surveys published in 1995 and 1996 respectively have shown that barbiturates were used in 56% of UK intensive care units and 33% of American intensive care units at that time. (89,90) Since 1974, case series data have suggested beneficial effects of barbiturate therapy on raised ICP. (95,96,97,98) These preliminary data suggest that ICP can be adequately controlled with barbiturates, neurological outcome can be improved, and mortality can be reduced.

Four well designed clinical trials have been published that involved the evaluation of barbiturate therapy for the management of head injury. (29,84,99,100,101) Two studies assessed prophylactic administration of barbiturates or their use in initial therapy for ICP elevations. Ward et al. performed a randomized, controlled trial of pentobarbital versus no pentobarbital in 53 head-injured patients with acute intradural hematoma or whose best motor response was abnormal flexion or extension. (99) Although the mean ICP and temperature were lower in the barbiturate group, hypotension (SBP less than 80 mm Hg) was significantly more common in the treated patients (54% versus 7%, $p < 0.05$), and may have reduced CPP. (99) There was no significant difference in 1-year Glasgow Outcome Scale (GOS) score between the groups. (99) Schwartz et al. conducted a prospective, randomized, single-blind trial comparing a load and continuous infusion of pentobarbital to 1 g/kg of 20% mannitol plus additional boluses in 59 patients with severe head injuries and raised ICP for greater than 15 minutes. (84) Pentobarbital was less effective than mannitol at controlling ICP with 68% of pentobarbital patients and 39% of mannitol patients requiring a second drug for treatment of ICP (RR = 1.75 95% CI 1.05-2.92). (84) This study failed to show a difference in mortality between the two groups (RR = 1.21 95% CI 0.75 - 1.94). (84) Levy et al. performed a randomized, controlled trial in head injury patients comparing pentobarbital and etomidate for control of raised ICP. (100) This trial was stopped after 7 patients were enrolled due to patients in the etomidate group developing renal failure. (100) The final trial is a prospective, randomized, double-blind multicentre trial published by Eisenberg et al. in 1988. (29) In this study, 73 patients with severe head injury (GCS 4-8) and intractable elevations in ICP were randomized to receive high dose pentobarbital 10 mg/kg over 30 minutes, followed by 5 mg/kg/h for 3 hours, and a 1 mg/kg/h infusion versus conventional therapy (no pentobarbital). (29) Serum pentobarbital levels of 30-40 mg/L were attempted. The primary outcome in this trial was controlled ICP less than 20 mm Hg. A smaller proportion of patients in the pentobarbital group had uncontrolled ICP (68% vs. 83%, $p = 0.22$), although this was not statistically significant. (29) The authors reported that the likelihood of survival in barbiturate responders was 92% at one month compared with 17% for non-responders. (29) Unfortunately the design of this study and others did not enable a conclusive determination on the effect of barbiturates on death or adverse neurological outcome. (1, 29)

A recent Cochrane Collaboration meta analysis examined the effects of barbiturates on outcome after TBI found no effect on mortality or morbidity (Table 4). (101) These data concur with an earlier meta analysis by Roberts et al. which also found no beneficial effect of barbiturates (Table 4). (102) Thus, all the data to this point have failed to show a beneficial effect on outcome with barbiturates in head injury. Unfortunately, the risk of hypotension was significantly higher than no therapy and translated to a fall in BP in 1 of every 4 patients treated. (101,102) Thus, if barbiturates are to be used for refractory increases in ICP, the pentobarbital regimen by Eisenberg should be followed. (1) According to the BTF Guidelines, barbiturate therapy may be considered in hemodynamically stable salvageable severe TBI patients with elevated ICP refractory to maximal medical and surgical therapy. (1) The pentobarbital infusion should be titrated to pentobarbital levels of 30-40 mg/L or preferably burst suppression on EEG. (93,103). It is important to monitor for hypotension, and vasopressor agents should be readily available during the loading period to support MAP and maintain a CPP greater than 70 mm Hg. (93)

Table 4. Meta analyses of therapeutic interventions for TBI

Intervention	Author, Year (ref)	Death		Death or disability (PVS or SD)		Post-traumatic Seizures		Adverse effect(s)	
		Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Barbiturates	Roberts 2000 (101)	48/105 (46%) RR = 1.09 (0.81-1.47)	43/103 (42%)	34/68 (50%) RR = 1.15 (0.81- 1.64)	29/67 (43%)			Hypotension RR = 1.80 (1.19-2.70) NNH = 4	

	Roberts 1998 (102)	37/64 (58%) RR = 1.12 (0.81-1.54)	32/62 (52%)	16/27 (59%) RR = 0.96 (0.62- 1.49)	16/26 (62%)		Hypotension RR = 1.80 (1.19-2.70) NNH = 4
Anticonvulsants	Schierhout 2000 (111)	95/540 (17.6%) RR = 1.15 (0.89-1.51)	78/514 (15.2%)	Phenytoin 67/208 (32.2%) RR = 0.96 (0.72- 1.39)	66/196 (33.7%)	Early (< 7 days) 22/456 (4.8%) RR = 0.34 (0.21-0.54) NNT = 10 Late (> 7 days) 65/499 (13.0%) RR = 1.28 (0.90-1.81)	Skin Rash 30/292 (10.3%) RR = 1.57 (0.57-39.88)
				Carbamazepine 44/75 (58.7%) RR = 1.49 (1.06- 2.08)	30/76 (39.5%)	49/482 (10.2%)	
Induced Hypothermia	Signiori 2000 (116)	31/79 (27%) OR = 0.67 (0.38-1.17)	41/116 (35%)	31/79 (39%) RR = 0.39 (0.20- 0.74) NNT = 4 (3-13)	49/79 (62%)		
Corticosteroids	Alderson 1997 (128)	396/1061 (37%) OR = 0.91 (0.74-1.12) ARR = 1.8% (- 2.5 - 5.7)	296/836 (35%)	651/977 (67%) OR = 0.90 (0.72- 1.11)	471/751 (63%)		Infections 126/ 447 (28%) OR = 0.92 (0.69-1.23) GI Bleeding 10/672 (1.49%) OR = 1.05 (0.44-2.52)
	Alderson 2000 (129)	410/1194 (34%) RR = 0.96 (0.85-1.08) ARR = 1.3% (- 2.5-5.2%)	301/925 (33%)	505/927 (55%) RR = 1.01 (0.91- 1.11)	340/701 (49%)		Infections 126/447 (28%) RR = 0.94 (0.76-1.16) GI Bleeding 18/837 (2.2%) RR = 1.11 (0.54-2.26)

Anticonvulsant Prophylaxis

The incidence of generalized seizures in patients suffering a head injury is 5%-10%. (10) The incidence of post-traumatic seizures (PTS) is higher in patients with a GCS less than 10, cortical contusion, depressed skull fracture, subdural hematoma, epidural hematoma, intracerebral hematoma or penetrating head wound. (1) PTS have been classified into early (occurring within 7 days of injury) or late (occurring after 7 days following injury) seizures. (1) In the convalescent period following TBI, seizures may exacerbate secondary injury by increasing ICP, increasing CMRO₂, CBF, CBV, lowering MAP, and potentially lowering CPP to worsen cerebral oxygenation. (10,11) Seizures may also lead to complications such as exacerbation of head injury, aspiration, nosocomial pneumonia, and a generally poorer overall outcome. For these reasons, and based on positive results from early retrospective trials, seizure prophylaxis was commonly prescribed by U.S. neurosurgeons for head-injured patients in the 1970s. (104) However, potential drawbacks of routine anticonvulsant prophylaxis can include dose-related CNS and gastrointestinal adverse effects, and idiosyncratic effects ranging from a mild rash to Steven-Johnson's Syndrome. (1)

One of the earliest randomized, controlled trials conducted to study the effect of phenytoin prophylaxis on the development of early and late PTS prophylaxis was performed by Young et al. in 1983. (105) In this study, 244 patients with head injuries were randomized to receive phenytoin or placebo and followed for two years. Patients received an 11 mg/kg IV loading dose, followed by IM or oral dosing guided by daily plasma phenytoin sampling in an attempt to achieve target plasma phenytoin levels of 40-80 umol/L. (105) According to the authors, there was no apparent difference in the incidence of early or late seizures between the treatment (3.7% and 12.4%) and the control (3.7% and 10.8%) groups. (1,105) This lack of apparent difference may be explained by the low incidence of seizures in the placebo group, which reduced the power of the trial to detect a difference. (1,105) During the early phase of the study, serum concentrations were obtained every 24 hours, and 78% of patients had plasma phenytoin concentrations of at least 40 umol/L. (105) Moreover, none of the patients with phenytoin plasma concentrations above 48 umol/L experienced a seizure. (105)

In 1990, Temkin et al. performed the largest prospective, randomized, double blind, placebo-controlled trial evaluating the effectiveness of phenytoin for the prevention of PTS in patients with severe head injuries. (106) In this study, 404 patients were randomized to receive a phenytoin 20 mg/kg IV loading dose followed by IV, oral, or nasogastric maintenance dosing that was guided by thrice weekly plasma phenytoin concentrations in the ICU, weekly on the ward, and at 1, 3, 6, 9, and 12 months during the 24 months follow-up. The daily doses varied considerably throughout the study and ranged from 200-1200 mg/d IV or orally, and up to 2600 mg/d given via the nasogastric route. The target phenytoin concentrations were 40-80 umol/L (total) or 3-6 umol/L (free). The incidence of early PTS was found to be significantly lower in the treatment group (3.6% (95% CI 2.3-4.9) versus 14.2% (95% CI 11.6-16.8), (p<0.001), RR = 0.27 (95% CI 0.12 to 0.62), number needed to treat (NNT) 10 (95% CI 8-18)) to prevent one early seizure. No significant reduction in late PTS between groups was observed. Eighty-one percent of patients had attained free phenytoin plasma concentrations

between 3.0-7.9 mmol/L following the loading dose, while at one week only 45% of measured plasma concentrations were within the same range. At the scheduled outpatient visits starting at one month, levels were at least therapeutic in 70% of patients. The drop in plasma phenytoin concentrations may have been due to early under-dosing and/or previously described pharmacokinetic alterations in severe TBI patients affecting protein binding and/or phenytoin metabolism. (107,108) There was a significantly higher incidence of rashes causing drug discontinuation in the phenytoin group (8.2 % versus 2.0%, ($p<0.01$), number needed to harm (NNH) of 17)). Using the initial Temkin data, for every 1000 patients treated with phenytoin, 111 seizures would be prevented and 62 patients would be expected to discontinue therapy as a result of the development of a rash. The Temkin trial had greater statistical power than the Young trial and likely showed a benefit because the population was at higher risk for seizures than those in the Young trial. The Temkin trial data have been re-analyzed to investigate the incidence of adverse effects during the first 2 weeks of therapy. (109) Based upon this new analysis, the overall incidence of adverse effects was found to be similar in the two groups (9% for phenytoin vs. 6% for placebo, $p=0.52$) as was the incidence of rash during the first week (0.6% vs. 0%, $p=1.0$). (109) Given that there is no difference in adverse effects between phenytoin and placebo, decisions on the use of 7 days of phenytoin prophylaxis should be made based on the clinical significance of the effects on seizure prevention and overall neurological outcome.

A more recent prospective, randomized, double blind trial by Temkin et al. involved a comparison of valproic acid with phenytoin for the prevention of early and late PTS in 379 patients with head injury. (110) Patients were enrolled if they had an immediate PTS, depressed skull fracture, penetrating brain injury or there was CT evidence of a cortical contusion, subdural, epidural, or an intracerebral hematoma. Patients were assigned to receive phenytoin therapy for 7 days, valproic acid therapy for 30 days, or valproic acid for 180 days. The incidence of early seizures was low and did not differ between the phenytoin and pooled valproic acid groups (1.5% versus 4.5%, $p=0.14$), $RR = 2.9$ (95% CI 0.7 - 13.3)). Due to the high upper confidence interval, the study did not have the power to exclude a potentially clinically significant inferior effect of valproic acid. The incidence of late seizures was not different between the groups, although there was a trend toward a higher mortality rate in patients receiving valproic acid vs. phenytoin (13.4% vs. 7.2%, $p=0.07$, $RR = 2.0$, 95% CI 0.9 - 4.1). For these reasons, valproic acid cannot be routinely recommended for the prevention of PTS until more data are available.

The Cochrane Collaboration group has published a recent meta analysis identifying 10 eligible randomized controlled trials involving 2,036 patients who were randomized to anticonvulsant therapy or placebo for PTS prophylaxis. (111) Data on early seizure frequency available from 4 published trials (890 patients) suggested that anticonvulsant agents reduced the incidence of early PTS but not late PTS, and failed to show a reduction in corresponding mortality (Table 4). Neither phenytoin prophylaxis nor carbamazepine prophylaxis resulted in a reduction in death and neurological disability for treated versus untreated patients (Table 4). Based on the trend towards an increase in death and neurological disability in this meta analysis, carbamazepine may actually be expected to increase death or neurological disability; however, the clinical significance of this finding is difficult to determine (Table 4). The analysis failed to rule out a clinically significant increase in skin rashes. Thus, based on the current data, the prophylactic use of anticonvulsants to prevent late PTS is not currently recommended in the BTF Guidelines and Practice Parameters by the Brain Injury Special Interest Group of the Academy of Physical Medicine and Rehabilitation. (1,112) Phenytoin is considered acceptable therapy for the prevention of early PTS; however, the current data do not support a reduction in overall mortality or death and neurological disability. (1,111) If phenytoin is used to prevent early PTS, a loading dose of 20 mg/kg, followed by an aggressive maintenance dose of 5-7 mg/kg/d (ideal body weight) should be used during the first week of therapy to attain target plasma phenytoin concentrations of 40-80 $\mu\text{mol/L}$ (total) or 4-8 $\mu\text{mol/L}$ (free) in this hypermetabolic patient population. (107,108)

Experimental Therapies for TBI

Induced Hypothermia

Fever is common in TBI patients, increases the body's metabolic rate, and is associated with worse neurological outcomes in TBI patients. For these reasons, induced therapeutic hypothermia has been used experimentally and in clinical trials as a method to reduce ICP and CMRO_2 in an attempt to improve neurological outcome after TBI. (1) The mechanism of protection conferred by induced hypothermia is unknown. Originally it was thought to be due to a reduction in CMRO_2 (113); however, hypothermia may also influence the excessive post-traumatic release of excitatory neurotransmitters (114), and attenuate opening of the blood-brain barrier. (115,116) Potential risks of induced hypothermia include pneumonia, sepsis, coagulation abnormalities, myocardial ischemia and atrial fibrillation. (116,117)

A reduction in body temperature from 37°C to 32°C reduces CMRO_2 by approximately 10%. (10) A preliminary prospective trial in severe head injury revealed that mild hyperthermia to 33.5-34.5°C significantly reduced ICP and increased CPP in patients refractory to high-dose barbiturate therapy. (118) In another study involving 33 severe head injury patients with refractory increases in ICP who received deferred moderate therapeutic hypothermia to 32-33°C, this body temperature reduction was found to reduce ICP and CBF by 40 % ($p<0.004$) and 26 % ($p<0.021$), respectively. The survival rate was also found to be higher in the treatment group ($p<0.05$). (40) More recently, Marion et al. completed the largest prospective,

randomized, double blind trial in 82 severely head-injured patients. (119) Body temperatures were reduced to 32-33°C approximately 10 hours after their injury, and these temperatures were maintained for 24 hours. Among patients with a GCS of 5-7, hypothermia was found to be less likely associated with a poor outcome of death, vegetative state, or severe disability (GOS of 1-3) compared to normothermia at 3 months (63% versus 83%, adjusted RR = 0.2 (95% CI 0.1-0.9), NNT of 5), and 6 months [45% versus 67%, adjusted RR = 0.2 (95% CI 0.1-0.9), NNT of 5], but not at 12 months (38% versus 62%, adjusted RR = 0.3 (95% CI 0.1-1.0)).

To determine the impact of induced hypothermia on mortality and neurological outcome, the Cochrane Collaboration conducted a meta analysis of 8 randomized controlled trials. (41,116,118,119,120,121,122,123,124) Trials were stratified into two groups: those that looked at active immediate hypothermia or deferred hypothermia. (116) Meta analysis failed to show a benefit of active, immediate hypothermia versus normothermia on mortality; however, a 61% reduction in the risk of death or severe disability was observed (Table 4). This translates in to a NNT of 4 (3-13) to prevent one patient from dying or being disabled. This apparent clinical benefit should be interpreted cautiously as the result may be due to publication bias. Only one trial of 33 patients involved an assessment of deferred hypothermia and reported deaths and GOS at 6 months. (118) This trial failed to show a significant difference in the risk of death (50% versus 82%, OR = 0.21 (95% CI 0.04-1.5)) or death or severe disability (63% versus 94%, OR = 0.10 (95%CI 0.01-1.00)). (116,118) Larger trials are necessary to confirm or refute the effect of induced or deferred hypothermia on long-term outcomes. All of the above trials involved reducing body temperatures to a range of 30-34.5°C for a maximum of 48 hours.

There are no published data to suggest a target cooling temperature, or ideal duration of cooling. However, Bernard et al. recently reported that a moderate hypothermia of 30-33°C for 8 days provided a satisfactory neurological outcome in 20 (47%) of 43 severely head-injured patients. (125) In this study there was a high incidence of nosocomial pneumonia (45%) and hypokalemia on cooling induction, and a decrease in total WBC and platelet counts over 10 days. (125) Another recent trial evaluated mild hypothermia (34°C) for 48 hours involving 16 severely head-injured patients in whom ICP was maintained below 20 mm Hg with conventional therapies. (126) There was no difference in neurological outcome and the authors concluded that mild hypothermia does not convey any benefit over normothermia for those patients with ICP maintained at less than 20 mm Hg using conventional therapies. (126) The potential drawbacks of induced hypothermia can include the induction of shivering which can increase CMRO₂, CERO₂, ICP, and lower CPP. To overcome this problem patients often require pharmacological paralysis with its inherent risks of prolonged paralysis and weakness. Controversies surrounding induced hypothermia will hopefully be resolved when a National Acute Brain Injury Study of hypothermia is published later this year. This study involves an examination of the effect of hypothermia (32-33°C) for 48 hours on GOS at 6 months in 392 severely brain-injured patients. (127)

Corticosteroids

Our ability to draw conclusions from existing studies of corticosteroids in TBI has been limited due to poor study design including a lack of control groups and blinding, inadequate sample sizes, and drug dosing inconsistencies. (128) Although corticosteroids are effective in reducing cerebral edema in patients with structural brain damage, these agents have not been shown to ameliorate increased ICP nor improve long-term outcomes. This has been thought to be due to the inability of steroids to prevent early cytotoxic edema and may also be related to corticosteroid-induced hyperglycemia, increased infection rates and/or gastrointestinal bleeding. (1,128)

Two meta analyses involving an assessment of corticosteroid trials have been reported. (128,129) In one analysis, 19 trials involving corticosteroid use for 2295 TBI patients were reviewed. (129) Mortality data extracted from 16 trials failed to show benefit on mortality, and data from 9 trials failed to show benefit on the aggregate endpoint of death or disability (Table 4). Another meta analysis that found similar results included many of the same trials, but had more stringent exclusion criteria. (128) Mortality data from 13 randomized trials involving 2073 patients failed to show benefit on mortality, and data from 10 trials failed to show benefit on the aggregate endpoint of death or disability. Both analyses failed to show a difference in infection rates and gastrointestinal bleeding between those who received corticosteroid and those who did not. It is important that although these data fail to show a significant benefit of corticosteroids on outcome, they also fail to exclude a potentially clinically significant absolute mortality reduction of up to 5.7%. (128) Even pooled together, the current trials are too small to support or refute a clinically important benefit from corticosteroids. Although a very large, multicentre trial would be required to solve this clinical dilemma, such a trial may be justified based on the clinical impact of the problem and the widely practicable treatment. (128) The current BTF Guidelines state, however, that corticosteroids are not recommended in TBI patients to lower ICP or improve outcome. (1) Despite that recommendation and the lack of evidence to support their use, the recent survey from Marion et al. suggests that 19% of U.S. Neurosurgeons would use corticosteroids in this setting. (91) The routine use of corticosteroids in TBI patients should be avoided until supported by clinical trial evidence.

Indomethacin

Indomethacin is a non-steroidal anti-inflammatory agent with unique effects on cerebral blood flow physiology that may be of benefit in reducing elevated ICP in TBI patients. Data from animal models and randomized, controlled studies with pre-term infants have shown that IV indomethacin produces rapid, significant reductions in cerebral blood flow (CBF). (47) Controlled studies of IV indomethacin in normal volunteers show a reduction in CBF from 26-40%. (47) Case series involving severe TBI patients suggest that indomethacin IV boluses of 30-50 mg reduce ICP by 37-52%, reduce CBF by 22-26%, with a modest 14% increase in cerebral perfusion pressure (CPP). (47) The onset of effects is almost immediate, and peaks in 1-5 minutes. The duration of ICP control is at least 4 hours and may be as long as 30 hours with a continuous infusion (CI). (47) ICP returns to baseline levels after the infusion is stopped. (47) No significant adverse effects have been reported but short-term changes in sensitive physiologic indicators of cerebral ischemia are of potential concern. Using indomethacin for ICP control may be potentially harmful to patients who already have normal or high CEO_2 or impaired autoregulation. In this subgroup, indomethacin may decrease CBF to ischemic levels that may not be overcome by a subsequent increase in CEO_2 . Indomethacin may also cause coronary ischemia in patients with ischemic heart disease, especially during anemia, hypoxemia, hypotension, systemic shunting, or impaired CEO_2 . For these reasons, some have suggested that indomethacin should not be used in patients with low SjvO_2 (less than 60 %), low CMRO_2 (less than 40 mL/100g/min), signs or symptoms of cerebral vasospasm, cardiac ischemia, renal failure, or bleeding ulcer. (130)

Important efficacy and safety issues regarding indomethacin use in TBI patients must still be addressed before it can be generally recommended for ICP control. Normal volunteer dose-response studies with IV bolus, CI, and PR dosing will characterize the pharmacodynamics of indomethacin on normal cerebral physiology. The effects of indomethacin on cerebral oxygenation in patients without luxury perfusion or those receiving therapeutic hyperventilation need to be determined. The effect of indomethacin on ICP and subsequent cerebral oxygenation must be studied, and the influence of these effects should be documented using functional neurological outcome scales. Thus, despite encouraging preliminary results, IV indomethacin should only be considered an experimental treatment for control of refractory ICP in TBI patients. Larger, well-designed randomized trials in TBI patients will provide more efficacy and safety data and delineate the effects of indomethacin alone or in combination with other proven, effective, or experimental therapies. Once these concerns have been addressed, larger outcome studies will ultimately be needed to determine the role of indomethacin for ICP control in TBI patients.

Neuroprotection

As mentioned previously, the secondary injury cascade is a complex biochemical loop that results in propagation of neurological injury. (Figure 1) Laboratory studies with numerous agents identified potential therapeutic targets for neuroprotection following TBI. (131) However, the positive effects shown in animal models have not been replicated in clinical trials. Some of these clinical investigations progressed to completion; however, many were prematurely halted due to interim "futility analyses" or due to concerns with safety. This has led to many theories regarding why these discrepancies occur including a lack of sensitivity in outcome measures, improper timing of therapeutic intervention, an inability to translate injury mechanisms in animals to human head injuries, poor brain penetration of drugs or inadequate doses used; and insufficient safety and tolerability investigation of the agent in question prior to the study. (131) There are many questions that still need to be answered including refining our understanding of the pathophysiology of TBI and the timing of these events. This section is devoted to a discussion of neuroprotective agents both past and present.

Increases in intraneuronal calcium seen with TBI initiates a cascade of biochemical events that can eventually result in cell lysis and death. Calcium-channel blockers in experimental models attenuated the increase in intracellular calcium concentration and thereby arresting neurological damage. (18) Nimodipine is a "cerebroselective" dihydropyridine calcium channel blocker that is approved by the Food and Drug administration to decrease the neurological morbidity following aneurysmal subarachnoid hemorrhage (SAH). This agent blocks the L-type calcium channel. The postsynaptic L-type channel remains open during depolarization to allow for excessive calcium accumulation. Blocking this channel may prevent the calcium buildup and it may have vasodilatory effects on cerebral vascular smooth muscle. Two large randomized, controlled trials have been performed to study the effect of nimodipine on the outcome of severe head injury, HIT I and HIT II. (132,133) Both trials showed a modest and an insignificant increase in the proportion of favorable outcomes in patients treated with nimodipine. A reanalysis of pooled data from both the HIT I and HIT II trials using IV nimodipine found that the overall benefit of treating unselected head injured patients with nimodipine is unlikely to be clinically relevant. (134) However a subgroup analysis of the HIT II trial suggested that there could be a possible protective effect of nimodipine in patients with traumatic SAH. (133) Another prospective, double-blind trial conducted in Germany randomized 123 TBI patients with a traumatic SAH to nimodipine (2 mg/h) or a matched placebo intravenously for 7 to 10 days, followed by oral treatment (360 mg daily) until day 21. (135) Patients treated with nimodipine had a significantly less unfavorable outcome (death, vegetative survival, or severe disability) at 6 months than placebo-treated patients (25% vs. 46%, $p=0.02$, OR 0.39, 95% CI 0.18-0.86). Therefore, due to these promising preliminary results, nimodipine is currently being investigated in a Phase III trial in patients with traumatic SAH with GCS 4-15.

Activation of the presynaptic N-type calcium channel in the nerve terminals is the leading cause of excitatory amino acid

release during ischemia. Therefore, blockade of this channel might reduce this excitotoxic process. The omega-conopeptide SNX-111, obtained from a carnivorous marine snail, is a potent antagonist of the voltage-gated N-type calcium channel and has demonstrated significant neuroprotective effects against neuronal injury. (136,137,138) However, the limiting adverse effect of this agent was hypotension, which could possibly lower CPP and affect outcome. This trial was halted due to a futility analysis indicating that the drug could not be safely used outside a controlled clinical trial setting. Following injury, release or formation of highly reactive free radicals may produce secondary damage to cellular membranes. This type of injury occurs through a process called lipid peroxidation, which is accelerated in the presence of free reactive iron. (18) Endogenous defense mechanisms and antioxidants were identified that scavenged free radicals. These systems include; superoxide dismutase (SOD), tocopherols, ascorbic acid, and retinoic acid. However, after injury the endogenous levels of these systems are depleted which permits progressive destruction of the cellular membrane. In the laboratory, scavenging of the superoxide anion SOD or polyethylene glycol (PEG)-conjugated SOD (PEG-SOD) has been shown to be beneficial following TBI. (139) A Phase II study included 104 patients randomly assigned to receive either placebo or PEG-SOD (2000, 5000, or 10,000 U/kg) intravenously as a bolus, an average of 4 hours after injury. At 3 months, 44% of patients in the placebo group were vegetative or had died, while only 20% of patients in the group receiving PEG-SOD were in these outcome categories ($p < 0.03$); similarly at 6 months, the same outcomes were 36% and 21%, respectively ($p = 0.04$). (140) From this study it appeared that PEG-SOD was a promising therapy. However, in a follow-up prospective, randomized, double-blind, placebo-controlled multicentre study of 463 patients treated within 8 hours of injury, no statistically significant difference in neurological outcome or mortality was observed between patients treated with PEG-SOD and those receiving placebo. (141) Therefore the use of PEG-SOD in clinical practice was abandoned.

A novel group of compounds, the 21-aminosteroids ("lazaroids"), also emerged as potent inhibitors of oxygen free radical-induced, iron-catalyzed lipid peroxidation. One of these, tirilazad mesylate (U-74006F), was selected for clinical investigation in various models of neurological injury. Preclinical models found that tirilazad improved neurological outcome when given between 5 minutes and 3 hours after injury. (142,143) The Phase III trial of tirilazad evaluated a cohort of 1120 head-injured patients. (144) Six-month outcomes for the tirilazad and placebo-treated groups for the Glasgow Outcome Scale categories of both good recovery and death showed no significant difference. However, subgroup analysis suggested that tirilazad mesylate may be effective in reducing mortality rates in males suffering from severe head injury with accompanying traumatic SAH. The investigators also described problems with imbalances in prognostic variables such as pretreatment hypotension, pretreatment hypoxia, and the incidence of epidural hematomas. (144) This study further emphasized the heterogeneous nature of TBI and the need for better randomization strategies to allow for a more homogenous study sample.

Excitotoxic mechanisms due to over-activity of the amino acid neurotransmitters glutamate and aspartate may be responsible for brain damage after injury. Glutamate activates the NMDA receptor that results in failure of the cellular ionic pump. Pharmacological antagonists of excitatory amino acids represent the most highly investigated class of agents following TBI. The competitive NMDA-receptor antagonist, CGS19755 (Selfotel) has been evaluated in the clinical setting with data reported from two phase III clinical trials. (145) A total of 693 TBI patients with a GCS of 4-8 and at least one reactive pupil were randomized to placebo or an intravenous infusion of 5 mg/kg of Selfotel once daily for 4 days. Due to possible increased deaths and serious brain-related adverse effects in the treatment arms of the two head injury trials and in two stroke trials, the Safety and Monitoring Committee stopped the trial prematurely. An interim efficacy analysis also indicated that it would be futile to continue the trial because the likelihood of demonstrating success with the treatment arm was almost nil. In the final analysis there was no statistically significant difference in mortality between the treatment groups. Cerestat (CNS 1102), a noncompetitive NMDA-receptor antagonist has also been evaluated in human TBI and did not show a positive effect. (131) CP-101,606 is a postsynaptic antagonist of the glutamate-mediated NR2B subunit of the NMDA receptor. A safety evaluation of CP-101,606 in patients with moderate or mild TBI or hemorrhagic stroke has been reported. Patients began receiving treatment within 12 hours of brain injury. The drug/placebo was administered by intravenous infusion for up to 70 hours. All the patients tolerated the drug, and there were no clinically significant cardiovascular, psychotropic, or hematological complications. (146) This agent is currently in Phase III testing and results are not yet available.

Some of the other agents currently being investigated include cyclosporine and magnesium. Cyclosporine transiently inhibits the opening of the mitochondrial permeability transition pore and maintains calcium homeostasis in isolated mitochondria. (147) Animals who received cyclosporine either 5 minutes before injury or immediately following injury show a significant reduction in the amount of cortical damage 7 days after TBI. (148) Another animal model administered a 20 mg/kg intraperitoneal bolus of cyclosporine or vehicle 15 minutes post injury found that all animals receiving cyclosporine demonstrated a significant reduction in lesion volume. (147) Cyclosporine was also shown to inhibit calcium-induced axonal damage when administered 30 minutes after injures. (149) These investigations suggest that there is a therapeutic window for the use of drugs targeting mitochondria and energy regulation in traumatic brain injury. (149) However, it is yet to be seen if these positive laboratory results will translate into significant clinical benefit.

Magnesium is another agent now being investigated for its potential neuroprotective properties. An animal model has been used to demonstrate that magnesium plays a role in neuroprotection following severe diffuse traumatic axonal brain

injury. Magnesium was shown to significantly improve motor outcome when administered up to 24 hours after injury. As would be expected, early treatments provided the most significant benefit and repeated administration beyond 24 hours post injury did not provide additional effects. (150) Magnesium appears to be promising but needs further evaluation before being tested in clinical trials.

Due to the ongoing high morbidity and mortality associated with conventional treatment of severe TBI, novel therapeutic strategies are being developed. One of these strategies is "Lund Therapy" of posttraumatic brain edema, named after the Lund University Hospital in Sweden. (151) This therapy attempts to prevent cerebral hypoxia while simultaneously counteracting transcapillary filtration. The Lund treatment protocol includes the following: 1) preservation of normal colloidal-absorbing force; 2) reduction in intracapillary pressure through a reduction in systemic blood pressure by antihypertensive therapy (metoprolol combined with clonidine); and 3) simultaneous, moderate constriction of precapillary resistance vessels with low-dose thiopental and dihydroergotamine. A cohort of 53 consecutive severe TBI patients admitted from 1989-1994 who were treated with Lund Therapy was compared with a historical control group of 38 severe TBI patients treated from 1982-1986. Fewer patients in the Lund Therapy group died (8% vs. 47%, $p < 0.0001$), and the ratio of patients with a favorable outcome was significantly higher in the Lund Therapy group ($p < 0.001$). (151) Due to methodological weaknesses of this study design, these hypothesis-generating results will need to be confirmed in a randomized clinical trial. (151)

The future of pharmacological neuroprotection is unclear at the present time. Several compounds have been tested and none have been shown effective in the clinical setting. The need for clinically effective agents is apparent especially in light of the devastating morbidity and mortality following severe TBI. It is the hope of many clinicians that these previous negative studies have taught us more about this injury and possible ways to plan clinical trials to avoid these same problems in the future.

Summary

TBI causes significant mortality, morbidity, and contributes substantially health care costs. Understanding normal cerebral physiology and altered physiology due to primary and secondary injury is essential to the identification of potentially useful therapies. Unfortunately, many of the specific therapies evaluated to date have not been shown to provide clinically important benefits.

CSF drainage and diuretics have failed to show a benefit on neurological outcome or mortality. Despite acute reductions in ICP and improvements in CBF with mannitol therapy, there are insufficient data to preclude either a harmful or beneficial effect on mortality. Hyperventilation may acutely control ICP; however, it has not been shown to improve outcome, and may worsen outcome if it is used routinely for long periods of time. Barbiturates may also improve surrogate physiologic markers in TBI, but they have failed to improve outcome, and are associated with a risk of hypotension in one out of four patients that may adversely affect CPP. Anticonvulsant prophylaxis has been shown to prevent early seizures after TBI, but failed to show a beneficial effect on outcome. Induced hypothermia reduces ICP, CBF, improves CPP, and meta analysis data have suggested that when used for less than 48 hours induced hypothermia is associated with a reduction in death or disability in TBI patients. Controversies regarding induced hypothermia may be resolved when a National Acute Brain Injury Study of hypothermia is published later this year. Meta analyses have failed to show a beneficial effect on mortality or neurological outcome in TBI patients treated with corticosteroids; however, a small but important beneficial effect of corticosteroids cannot be ruled out. Although a large clinical trial evaluating corticosteroids may be warranted, at this point routine corticosteroid therapy cannot be recommended.

Due to the disappointing results with specific therapies for TBI to date, specific experimental therapies and neuroprotective agents will continue to be evaluated. To date, many promising experimental neuroprotective strategies have not been proven beneficial in the clinical setting, but further studies are needed. Studies comparing overall management strategies that include therapies not shown to be harmful would also be beneficial and may enhance the effect size shown in the experimental group. Thus, until more data are available, specific goals of therapy published in TBI guidelines and consensus articles should be followed: 1) controlling ICP less than 20-25 mm Hg; 2) maintaining CPP at or above 70 mm Hg or MAP above 90 mm Hg in the absence of an ICP monitor; 3) optimizing cerebral oxygenation by ensuring normal coupling between $CMRO_2$ and CBF and maintaining CEO_2 below 42% ($CERO_2$ less than 40%); (1,32) and 4) preventing and/or treating cerebral and systemic complications of TBI is also essential in these patients.

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Pharmacological Management of Severe Traumatic Brain Injury: An Evidence-Based Review

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Abstract

Traumatic brain injury (TBI) accounts for almost one-half of all trauma fatalities and has a significant impact on mortality, morbidity, and health care costs. Understanding normal cerebral physiology and metabolic derangements due to primary and secondary injuries after TBI help to delineate cellular mechanisms of injury and identify potentially beneficial therapies. Neurological monitoring and adherence to objective, specific goals for initial resuscitation and support of the TBI patient are essential. Specific therapies such as cerebrospinal fluid drainage, diuretics, hyperventilation, barbiturates, and anticonvulsant prophylaxis have been studied. Many of these interventions have been empirically based on pathophysiologic rationale and have subsequently been implemented in the context of head-injury management protocols in an attempt to improve patient outcomes. Traditionally, studies evaluating TBI therapies have been limited by design flaws. However, larger better-designed trials have recently been undertaken, and meta-analytic techniques have also been employed to help establish the relative merit of various therapies for TBI. Unfortunately, early interest in many of these therapies has not translated into clinical benefits in well-designed trials. For these reasons, experimental therapies such as induced hypothermia, corticosteroids, indomethacin, and other neuroprotective strategies such as calcium channel blockers, antioxidants, 21-aminosteroids, antagonists of excitatory amino acids, cyclosporine, magnesium, and "Lund therapy" continue to be evaluated.

The purpose of this review is to provide the reader with a comprehensive review of the pathophysiology, neurological monitoring, therapeutic goals, initial resuscitation strategies, and treatment options for the TBI patient.

J Inform Pharmacother 2000;3:309-335.

Introduction

Trauma results in about 150,000 deaths in the United States each year, and approximately one-half of this mortality is specifically related to head injuries. (1) The 1-year survival rate following a head injury is lower in patients over 50 years of age, possess lower initial Glasgow Coma Scores and higher Injury Severity Scores, lack pupillary responses, reveal a hematoma on CT scan, and in those who demonstrate evidence of brainstem injury. (2) Although mortality is the principal endpoint, the long-term functional outcome following a head injury is also crucial. Tragically, approximately 200,000 people in the U.S. live with disabilities caused by traumatic brain injuries. (1) The economic impact of these injuries is also substantial. The initial treatment cost per severe head injury is estimated to be approximately \$150,000 U.S. and a 1990 report estimates total direct and indirect lifetime costs to be \$158 billion U.S. for all head injuries in the U.S. (3)

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It is now generally recognized that secondary as well as primary injury contributes to the morbidity and mortality of traumatic brain injury (TBI). Brain swelling and increased intracranial pressure (ICP) promote secondary injury, and it has been hypothesized that intracranial hypertension may be the primary cause of death in some patients. (4,5) Aggressive management protocols, including ICP control, have been shown to reduce the overall mortality and morbidity rate. (1,6,7,8) According to data from the Traumatic Coma Data Bank (TCDB), such protocols have resulted in an overall mortality reduction following severe head injury from 50% to 36%. (9) Despite these encouraging results, several currently applied therapies remain to be properly evaluated in well-designed trials and new pharmacological strategies to control ICP, improve cerebral oxygenation, and reduce morbidity and mortality are still needed to further improve patient outcomes.

The purpose of this review is to provide an overview of cerebral physiology under normal conditions and during TBI, provide an outline of monitoring strategies for TBI patients, review current treatment strategies to control ICP and optimize cerebral oxygenation in TBI patients, and discuss experimental therapies in the pharmacological management of TBI.

Normal Cerebral Physiology

Although the brain represents only 2% of total body weight, it utilizes 20% of the systemic oxygen consumption for the oxidation of glucose. (10,11) The metabolic rate of the brain is often expressed in terms of its rate of oxygen consumption (CMRO₂), which is approximately 3.5 mL/100g brain/min. (10,11) Approximately 15% of cardiac output is distributed to the brain (750 mL/min), and normal cerebral blood flow (CBF) in an adult remains relatively constant at 40-50 mL/100 g brain/min. (10,11) Under normal conditions, the brain has little energy reserve, so CBF is tightly coupled to CMRO₂ and brain function. As cerebral metabolism and oxygen consumption increase, metabolic autoregulation results in a parallel increase in CBF and cerebral oxygen delivery (CDO₂). (10) Cerebral blood flow is tightly regulated to metabolism in order to maintain oxygen supply in balance with oxygen demand, and to protect the brain from extremes in perfusion pressure due to

hypertension. Cerebral blood flow autoregulation permits cerebral vasculature to alter cerebrovascular resistance (CVR) to maintain a constant CBF despite variations in cerebral perfusion pressure (CPP). Accordingly, CBF is equal to CPP/CVR. (10,12) Cerebral perfusion pressure is determined by the mean arterial pressure (MAP), and ICP, thus CPP is equal to (MAP - ICP). (10,12) Under normal conditions, despite variations in MAP (between 50 and 150 mm Hg) and concurrent variations in CPP, CBF remains relatively constant due to alterations in CVR. Mean arterial pressure below 50 mm Hg may result in cerebral ischemia, while MAP above 150 mm Hg may result in capillary injury or edema. (10,11,12)

Intracranial pressure is measured most reliably from within the ventricle and is normally less than 15 mm Hg. The skull is a rigid compartment containing brain tissue (80%) cerebrospinal fluid (CSF) (10%), and blood volume (10%). (13) The Monroe-Kellie doctrine states that these incompressible structures within the cranial vault are in a state of volume equilibrium, and any increase in the volume of one component must be compensated for by one or more of the other components to ensure that intracranial volume remains constant. (14,15) Any disturbances in intracranial volume will alter ICP, while any increase in ICP will reduce CPP and may reduce CBF if alteration in CVR via autoregulation is not functional. Factors that normally influence cerebral autoregulation include carbon dioxide and oxygen. As PaCO₂ drops to between 20-80 mm Hg, there is a linear decrease in CBF. (10,16) Hypocapnia decreases CBF and hypercapnia increases CBF. (10,11,16) In fact, CBF increases 2-3% per mm Hg increase in PaCO₂ above 40 mm Hg. (10,11,16) Hypoxemia also affects autoregulation, and when PaO₂ drops below 50 mm Hg, CBF doubles. (10,11,16) The extraction of oxygen from the cerebral blood (CEO₂) is defined as the difference between arterial oxygen saturation (SaO₂) and jugular venous oxygen saturation (SjvO₂), thus CEO₂ is equal to SaO₂-SjvO₂. (17) Under normal conditions, SjvO₂ is 55-71%, and CEO₂ is relatively constant at 24-42%. (17) The cerebral extraction ratio (CERO₂) is defined as the ratio between cerebral oxygen consumption (CMRO₂) and cerebral oxygen delivery (CDO₂), CMRO₂/CDO₂. CERO₂ is practically expressed as (SaO₂-SjvO₂)/SaO₂. Normal CERO₂ is around 35% ± 10%. Major causes of decreases in SjvO₂ and thus increases in CERO₂ can be due to reduced cerebral oxygen delivery (CDO₂) or increased cerebral

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oxygen consumption (CMRO₂). The normal cerebral physiology can be summarized by the equations in Table 1.

Table 1. Normal Cerebral Physiology

Equations	Definitions
$CBF = CPP / CVR$	CBF: Cerebral blood flow
$CPP = MAP - ICP$	CPP: Cerebral perfusion pressure
$CBF = (MAP - ICP) / CVR$	CVR: Cerebral vascular resistance
$CEO_2 = SaO_2 - SjvO_2$	MAP: Mean arterial pressure
$CEO_2 = CMRO_2 / CDO_2$	ICP: Intracranial pressure
$DO_2 = (SaO_2 - SjvO_2) / SaO_2$	CBF: Cerebral blood flow
	CEO ₂ : Cerebral oxygen extraction
	SaO ₂ : Arterial oxygen saturation
	SjvO ₂ : Jugular venous oxygen saturation
	CERO ₂ : Cerebral extraction ratio of oxygen
	CMRO ₂ : Cerebral metabolic consumption of oxygen
	CDO ₂ : Cerebral oxygen delivery

Pathophysiology of TBI

Neurological complications from TBI can occur as a direct result of the primary injury, or may be caused by secondary injuries that follow within minutes to days. The primary injury is typically the result of a direct initial insult and the secondary injury is caused by the subsequent cascade of biochemical changes that are triggered by ischemia and result in a disruption of the normal central nervous system balance between oxygen supply and demand (Figure 1).

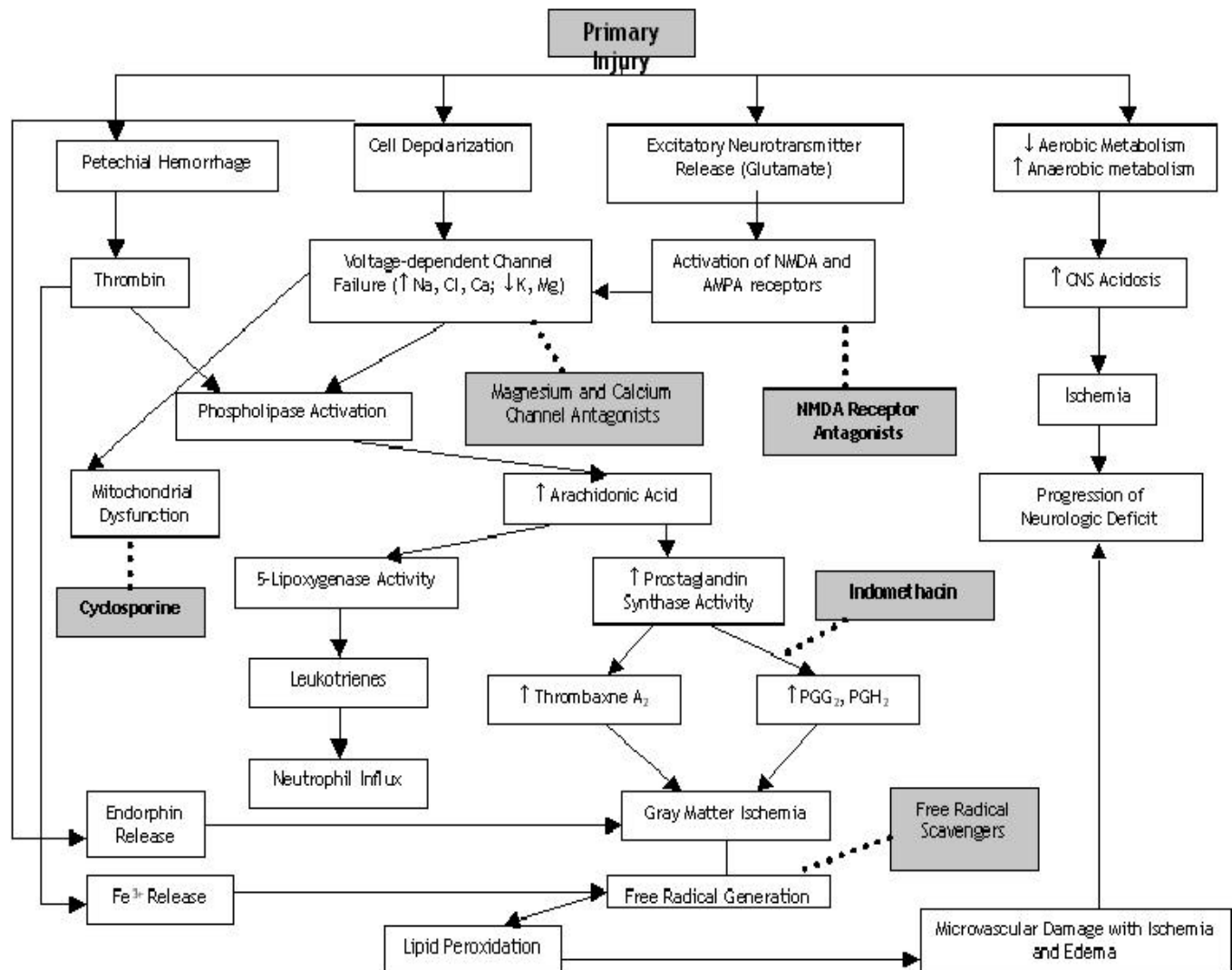
Following ischemia, cells release the excitatory amino acid glutamate and adenosine triphosphate (ATP) levels will decrease. Glutamate activates N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), kainate, and metabotropic receptors. (16,18) Activation of these receptors results in a failure of the cellular ionic pump with rapid influxes of calcium and sodium into the cell and subsequent depolarization. Calcium has several deleterious effects including cerebral vasospasm, mitochondrial dysfunction, and activation of proteases

and lipases. The effect of lipase stimulation is the formation of several arachidonic acid derivatives including thromboxane A₂ (TXA₂), prostacyclin (PGI₂), prostaglandin G₂, prostaglandin H₂ and leukotrienes. (16,18) The resulting effects of these arachidonic acid derivatives are platelet aggregation, vasodilation and oxygen free radical production with lipid peroxidation. Decreased ATP levels leads to a diminished ion gradient with increases in lactate and subsequent acidosis and ischemia. (18) The entire secondary injury process is a vicious cascade of biochemical changes that leads to further spread of the ischemic injury and neurological deficits. The causes of secondary injury include cerebral edema, expanding mass lesions, and cerebral vasospasm. (12) Other factors that may potentiate secondary injury include elevated temperature, seizures, and agitation. (12) The loss of cellular integrity from the ionic shifts may result in cytotoxic edema and vasogenic edema may also develop due to cerebral capillary endothelial damage. (12)

The swelling of injured tissue after TBI tends to peak within 72 hours of injury and leads to cerebral edema. The most detrimental consequence of this cerebral edema is increased ICP since it leads to significant morbidity and mortality. (1,4,5,6,7,8,10) If the CSF or cerebral blood volume cannot be reduced to compensate for the increased brain volume, the ICP will rise. The less compliant the brain is, the higher the ICP will rise for a given amount of cerebral edema. Raised ICP compresses brain tissue and decreases CPP, further increasing cerebral injury. (12) Cerebral injury affects autoregulation, which would normally help combat changes in pressure associated with neurological injury. (12) Autoregulation can be either impaired, or preserved at lower levels of CBF after TBI. Thus, the injured brain may be especially susceptible to hypotension that reduces CPP and causes cerebral ischemia in the early post-injury phase.

Cerebral metabolic consumption of oxygen is globally depressed in severely head-injured patients with systemic energy expenditure decreasing from 20% to 11% (10). The reduction in CMRO₂ is proportional to the severity of coma, as reflected by the Glasgow Coma Scale (GCS). (Table 2) (19,20)

Figure 1. Illustration of Secondary Neurologic Injury Cascade with the Potential Role of Indomethacin and Neuroprotective Agents



There are three scenarios describing cerebral oxygenation during the period of reduced CMRO₂. (Table 3) In approximately 45% of patients, there is normal coupling between the CMRO₂ and CBF. (10,11) Decreased neuronal metabolism and CO₂ production leads to a reduction in CBF that is proportional to the reduced CMRO₂ while the CERO₂ remains unchanged. (17) In this scenario, there is intact metabolic autoregulation and a balance between cerebral oxygen consumption and delivery. The second scenario is termed "oligemic cerebral hypoxia" or "misery

perfusion". Coupling between CMRO₂ and CBF is lost, and CBF is low relative to the needs of the brain. If cerebral oxygen delivery is reduced due to hypotension, systemic anemia, systemic hypoxemia, high ICP, cerebral vasospasm, or marked hypocapnia, the brain responds by increasing the extraction of oxygen to compensate, the S_{jv}O₂ will fall and the CERO₂ will increase. (10,17) However, a point will be reached at which further decreases in CBF cannot be compensated for by increased oxygen extraction and ischemia follows, manifested by a CERO₂ above 40%.

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Table 2. Glasgow Coma Scale

Neurologic Function	Response	Score
Eye Opening (/4)	Spontaneous	4
	To sound	3
	To pain	2
	No response	1
Best Motor Response (/6)	Obeys commands	6
	Localizes pain	5
	Flexion (withdraws)	4
	Abnormal flexion (decorticate rigidity)	3
	Abnormal extension (decerebrate rigidity)	2
	No response	1
Best verbal response (/5)	Oriented	5
	Confused conversation	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
TOTAL (/15)		(3-15)

(17) Within 6 hours of injury, there is a global reduction in CBF to ischemic levels in 13% of patients. (21) If there is a severe reduction of CBF for a sufficient duration of time, these ischemic changes will become irreversible and lead to brain tissue infarction. Increases in cerebral oxygen delivery after this point will not result in greater CEO2 because of permanent tissue damage. Under these conditions, the S_{jv}O₂ will actually increase and the CERO₂ will fall, indicating permanent damage. (10) To prevent cerebral ischemia, treatment strategies must focus on increasing cerebral oxygen delivery (CDO₂) or reducing oxygen consumption (CMRO₂). Major causes of reduced CDO₂ include systemic hypotension, increased ICP and thus low CPP, systemic anemia, systemic hypoxemia, cerebral vasospasm, or marked hypocapnia. (10) Major causes of increased CMRO₂ include agitation (e.g. pain, anxiety, or delirium), fever, and seizures. (10)

The final scenario is that called "relative cerebral hyperperfusion" or "luxury perfusion". Coupling between CMRO₂ and CBF is lost, and CBF is excessive to that required to meet the metabolic needs of the brain. (17) This increase in cerebral blood volume may contribute to a high ICP thus reductions in

cerebral blood volume or overall ICP are indicated. In this scenario, the S_{jv}O₂ is high, and the CERO₂ remains low. (17)

Neurological Monitoring in TBI Patients

Neurological monitoring in TBI patients may include physical and neurological examinations, ICP monitoring, S_{jv}O₂ monitoring, electroencephalographic (EEG) monitoring, and transcranial doppler (TCD) ultrasonography. (22,23) A complete physical and neurological examination including brainstem function, GCS, and cranial nerve function are indicated to establish the extent of the injury, and to establish a baseline for neurological monitoring. (22,23) The GCS is used to evaluate the level of consciousness according to eye opening, best motor response, and best verbal response. The admission or last known GCS is used to grade the severity of TBI. A GCS score of 13-14 indicates mild injury, a score of 9-12 indicates moderate injury, while a score of 3-8 indicates severe injury. (24) The GCS has also been shown to be a useful predictor of one-year survival and cognitive recovery. (2,24)

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Table 3. Cerebral Oxygenation Alterations After TBI

Scenario	CMRO ₂	CBF	CERO ₂	Comment
Intact metabolic autoregulation	↓	↓	↔	Normal coupling and extraction
Oligemic cerebral hypoxia (misery perfusion)	↓	↓↓	↑	Cerebral ischemia may cause secondary injury
Relative cerebral hyperperfusion (luxury perfusion)	↓	↑	↓	Excess CBV may increase ICP and cause secondary injury

CMRO₂=Cerebral metabolic consumption of oxygen, CBF=Cerebral blood flow, CERO₂=Cerebral extraction ratio of oxygen, CBV =Cerebral blood volume, ICP=Intracranial pressure

Although outcome benefits of ICP monitoring have never been assessed in a prospective, randomized clinical trial, it is nevertheless considered essential for the patient with severe TBI. (1) Increases in ICP have been associated with worse neurological outcomes, (5,25,26,27,28) and it has been suggested that intracranial hypertension is the primary reason for death in some patients. (4,5) Moreover, the use of intensive ICP-based management protocols have been associated with significant reductions in morbidity and mortality from TBI. (5,6,7,8,9,29) In one prospective, randomized controlled trial, mortality was shown to be significantly lower in patients for whom ICP was successfully controlled with barbiturate therapy. (29) However, there have been no prospective, randomized trials to compare outcomes using different treatment thresholds for ICP. (1) The investigators of a small, uncontrolled non-randomized trial reported an associated reduction in mortality in patients whose ICP treatment was initiated at 15 mm Hg versus treatment initiated at 20-25 mm Hg. (6) Uncontrolled co-interventions and potential biases in the trial design may explain these results. Another recently published study involved an examination of the relationship between ICP, CPP and outcome. (30) Juul et al. reviewed these parameters in a series of 427 patients who were enrolled in the randomized, double-blind trial of Selfotel, a NMDA receptor antagonist. They reported that treatment protocols should emphasize immediate treatment of ICP greater than 20 mm Hg and that CPP greater than 60 mm Hg had very little influence on patient outcome. (1) The likelihood of herniation due to high ICP may also depend on the

location of the intracranial mass lesion. (1,11,31) For example, lesions of the anterior temporal lobe can cause herniation at an ICP level of less than 15 mm Hg. (31) The Brain Trauma Foundation (BTF) guidelines contain recommendations for continuous ICP monitor placement in patients with a GCS of 8 or less with an abnormal admission CT scan, or in high-risk (age greater than 40 years, motor posturing, or systolic blood pressure under 90 mm Hg) severe head injury patients with a normal CT scan. Ventricular catheters connected to an external strain gauge are considered to be the most accurate, least costly, and most reliable method for monitoring ICP. The use of these catheters also allows for the therapeutic drainage of CSF. (1) The BTF and European Brain Injury Consortium (EBIC) Guidelines recommend 20-25 mm Hg as the upper threshold at which treatment to lower ICP should be initiated. (1,32) In summary, ICP monitoring helps determine prognosis, enables early detection of mass lesions, allows monitoring of interventions to lower ICP, enables CSF drainage to reduce ICP, and enables calculation and optimization of CPP.

Cerebral ischemia may be the single most important secondary event influencing outcome following severe TBI. (33) CPP is the physiologic variable driving CBF and energy delivery, and therefore it is closely related to ischemia. Reducing elevated ICP or artificially increasing the MAP can increase CPP. While there have been concerns that strategies to increase MAP to achieve a higher CPP may increase brain swelling and raise ICP, studies by Bouma and Bruce have shown that

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BP increases of as much as 30 mm Hg does not significantly alter ICP. (34,35) This phenomenon appears to exist regardless of whether or not patients had intact cerebral autoregulation. No prospective, randomized, controlled studies have definitively proven that intracranial hypertension, morbidity or mortality is reduced by maintaining CPP values at or above 70 mm Hg. (1) However, CPP has been shown to be strongly correlated to mortality, (36) and several investigators have also demonstrated an associated decrease in patient morbidity and mortality when CPP is actively sustained above 70 mm Hg. (37,38,39,40,41) One study involving 189 patients compared the effects of a CBF-targeted protocol that kept CPP over 70 mm Hg and PaCO₂ at 35 mm Hg, versus an ICP-targeted protocol that kept CPP above 50 mm Hg and PaCO₂ at 25-30 mm Hg. (42) The CBF-targeted protocol reduced the frequency of jugular desaturation from 50.6% to 30% (p=0.006). (42) This study was not powered to determine a difference in neurological outcome. (42) These preliminary data suggests that a CPP of at or above 70 mm Hg may reduce both global and regional ischemia and limit secondary injury. Therefore, the BTF and EBIC Guidelines suggest that CPP be maintained above 70 mm Hg. (1,32)

There is no practical method for measuring CMRO₂ or CBF in the ICU setting. Although jugular venous saturation monitoring does not give quantitative information about either CMRO₂ or CBF, it reflects the ratio between these two variables. By utilizing SaO₂ and S_{jv}O₂, the CEO₂ and CERO₂ can be calculated (Table 1), and the balance between CMRO₂ and CDO₂ can be determined (Table 2). In this way, it is possible to know if CMRO₂ and CBF are appropriately coupled, or if the injured brain is undergoing "oligemic cerebral hypoxia" or "luxury perfusion". The occurrence of one episode of jugular venous desaturation was associated with a two-fold increase in the risk of poor neurological outcome while multiple episodes were associated with a 14-fold increase in risk. (43) Monitoring of S_{jv}O₂ is useful because ICP and CPP are pressure monitoring strategies and may not detect cerebral ischemia. (44) Therefore some have advocated using jugular venous bulb saturation monitoring to optimize cerebral oxygenation. (44,45) It may also be especially useful in situations where ICP monitoring is not readily available or coagulation abnormalities contraindicate the use of ICP monitoring. (44,45) One prospective interventional

study involved a comparative outcome assessment of 353 patients with severe acute brain trauma who underwent both management of cerebral extraction of oxygen and cerebral perfusion pressure versus patients who underwent monitoring and management of cerebral perfusion pressure alone. At 6 months post injury, patient outcomes were significantly better in the group who underwent cerebral extraction of oxygen monitoring. (17) Monitoring of S_{jv}O₂ is considered to be very useful for monitoring therapies used in TBI patients. Therapeutic strategies such as hyperventilation and indomethacin may reduce ICP at the expense of inducing cerebral ischemia, and worsening secondary brain injury and neurological outcome (46,47). These acute therapies can be safely monitored using a jugular bulb saturation monitor that will detect a drop in S_{jv}O₂ and increased CERO₂ indicating cerebral ischemia. Drawbacks of jugular bulb catheter monitoring include the potential for complications, and the cost of the catheters themselves. There are technical difficulties associated with catheter placement, and anatomical structures close to the internal jugular vein can be injured during catheterization. (45) Once placed, the position of the catheter tip within the jugular bulb should be confirmed radiographically. (45) Complications of S_{jv}O₂ monitoring are rare, with a 4.5% incidence of carotid artery puncture, and 40% incidence of subclinical jugular thrombi. (48) In summary, jugular bulb monitoring is used to optimize cerebral oxygenation by providing information on CERO₂, and ensuring normal coupling between CMRO₂ and CBF during management of TBI. The BTF Guidelines acknowledge that jugular venous oxygen saturation monitoring may be useful by identifying cerebral ischemia induced by therapies such as hyperventilation. (1)

Electroencephalogram tracings closely correlate with CMRO₂. (10) In normal adults, infusion of barbiturates until the EEG becomes flat reduces the CMRO₂ by 50% to an average of 1.5 mL/100g brain/min. (49) Therefore it is useful in sedative titration in barbiturate coma. The EEG is also considered to be the best method for detecting seizure activity, and is especially useful in patients on paralytic agents or those suspected of having non-convulsive status epilepticus. (50) Vespa et al. recently reported their observations with the incidence and impact of nonconvulsive and convulsive seizures in a series of 94 moderate to severe TBI

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Table 4. Meta analyses of therapeutic interventions for TBI

Therapy	Author	Death		Death or disability (PVS or SD)		Post-traumatic Seizures		Adverse effect(s)	
		Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Barbiturates	Roberts 2000 (101)	48/105 (46%) RR = 1.09 (0.81-1.47)	43/103 (42%)	34/68 (50%) RR = 1.15 (0.81-1.64)	29/67 (43%)			Hypotension RR = 1.80 (1.19-2.70) NNH = 4	
	Roberts 1998 (102)	37/64 (58%) RR = 1.12 (0.81-1.54)	32/62 (52%)	16/27 (59%) RR = 0.96 (0.62-1.49)	16/26 (62%)			Hypotension RR = 1.80 (1.19-2.70) NNH = 4	
Anticonvulsants	Schierhout 2000 (111)	95/540 (17.6%) RR = 1.15 (0.89-1.51)	78/514 (15.2%)	Phenytoin 67/208 (32.2%) RR = 0.96 (0.72-1.39)	66/196 (33.7%)	Early (< 7 days) 22/456 (4.8%) RR = 0.34 (0.21-0.54) NNT = 10	65/434 (15.0%)	Skin Rash 30/292 (10.3%) RR = 1.57 (0.57-39.88)	18/276 (6.5%)
				Carbamazepine 44/75 (58.7%) RR = 1.49 (1.06-2.08)	30/76 (39.5%)	Late (> 7 days) 65/499 (13.0%) RR = 1.28 (0.90-1.81)	49/482 (10.2%)		
Induced Hypothermia	Signori 2000 (116)	31/79 (27%) OR = 0.67 (0.38-1.17)	41/116 (35%)	31/79 (39%) RR = 0.39 (0.20-0.74) NNT = 4 (3-13)	49/79 (62%)			Infections 126/ 447 (28%) OR = 0.92 (0.69-1.23)	131/460 (29%)
Corticosteroids	Alderson 1997 (128)	396/1061 (37%) OR = 0.91 (0.74-1.12) ARR = 1.8% (-2.5 - 5.7)	296/836 (35%)	651/977 (67%) OR = 0.90 (0.72-1.11)	471/751 (63%)			GI Bleeding 10/672 (1.49%) OR = 1.05 (0.44-2.52)	8/621 (1.29%)
	Alderson 2000 (129)	410/1194 (34%) RR = 0.96 (0.85-1.08) ARR = 1.3% (-2.5-5.2%)	301/925 (33%)	505/927 (55%) RR = 1.01 (0.91-1.11)	340/701 (49%)			Infections 126/447 (28%) RR = 0.94 (0.76-1.16)	131/460 (28%)
								GI Bleeding 18/837 (2.2%) RR = 1.11 (0.54-2.26)	11/703 (1.6%)

patients. (51) Overall, convulsive and nonconvulsive seizures occurred in 21 patients (22%), with 6 cases of status epilepticus. (51) All patients with status epilepticus died, compared with a mortality rate of 24% in the group without seizures ($p < 0.001$). (51) In more than half of the cases, the seizures were nonconvulsive and were diagnosed solely by EEG. (51) Moreover, the mean serum phenytoin blood concentration in patients with seizures was 66.4 $\mu\text{mol/L}$, which is considered to be within the usual therapeutic range for phenytoin. Thus, it can be seen that there is a significant occurrence of nonconvulsive seizures in TBI patients, and that these seizures may occur in the presence of appropriately dosed prophylactic phenytoin therapy. Although there is a valuable role for continuous EEG monitoring in the TBI

patient, continuous EEG monitoring is not routinely used in all centers.

Transcranial Doppler (TCD) ultrasonography measures cerebral blood flow velocity, which is a surrogate marker of CBF. (52) When flow through a vessel is constant, cerebral blood flow velocity increases inversely to the vessel's cross-sectional area. (52) Analysis of TCD waveform and blood flow velocity can indirectly provide information about CBF and ICP. The analysis of the velocities during the cardiac cycle is presented as a waveform. Current machines calculate a mean flow velocity and the pulsatility index (PI). The PI (equal to $[\text{systolic velocity} - \text{diastolic velocity}] / \text{mean velocity}$) is an index of vascular resistance. Therefore, this index would be

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elevated in patients with increased ICP. Vasospasm is defined as a mean flow velocity above 102 cm/sec. Transcranial doppler monitoring can be used to detect vasospasm, assess blood flow patterns, determine patency of cerebral vessels, and detect elevated ICP in TBI patients. (53) The most important limitation of TCD monitoring is the technical ability of the neurologist. (52) In summary, TCD is a non-invasive method that may be used to assess the adequacy of cerebral blood flow in an attempt to differentiate hyperemia from vasospasm and to assess the status of cerebral autoregulation in TBI patients. (52)

Goals of Therapy for TBI

The overall goals of management for TBI patients are to reduce mortality, morbidity, and improve long-term functional outcome. Secondary brain injury can be prevented and/or limited by optimizing cerebral resuscitation. Specific goals of therapy published in existing TBI guidelines and consensus papers include: 1) controlling ICP to less than 20-25 mm Hg (1); 2) maintaining CPP at or greater than 70 mm Hg or MAP above 90 mm Hg if an ICP monitor is not in place; 3) optimizing cerebral oxygenation by ensuring normal coupling between CMRO₂ and CBF and maintaining CEO₂ above 42% (CERO₂ above 40%); and 4) preventing and/or treating cerebral and systemic complications of TBI. (1,32)

Therapeutic Interventions for TBI

Initial Resuscitation

As with any trauma patient, the initial priorities are establishment of an adequate airway, breathing, and circulation. If the patient's level of consciousness is impaired to the extent that the airway cannot be protected, intubation is required. (22,23,54) Mechanical ventilation may be indicated in the setting of hypercapnic or hypoxemic respiratory failure caused by a decreased level of consciousness, atelectasis, pneumothorax, or pulmonary edema. Mechanical ventilation may enable brief hyperventilation that may be indicated for acute increases in ICP. Oxygen saturation should be maintained above 90 % and paO₂ above 60 mm Hg. (1,32,54)

Circulating volume must also be restored with packed red blood cells if the hematocrit is less than 30%, and isotonic (0.9%) saline for further fluid resuscitation. (22,23) Colloids (mannitol and albumin) and hypertonic saline (3% and 7.5%) have been studied for initial resuscitation; however data from prospective trials have not shown clinically significant advantages in resuscitation or neurological outcome. (55,56,57,58,59) Hypotonic fluids should not be used for initial fluid resuscitation, as they may lead to hyponatremia and a hypo-osmolar state that may exacerbate cerebral edema. The goal of fluid resuscitation and fluid maintenance should be euvolemia without reducing plasma osmolarity. (22,23,54) If fluids alone do not restore MAP to 90 mm Hg, inotropic and vasopressor agents such as dopamine, phenylephrine, and norepinephrine may be required. (54)

Adequate resuscitation is vital as SBP less than 90 mm Hg or hypoxia (apnea or cyanosis in the field or a PaO₂ less than 60 mm Hg) are strong independent risk factors for mortality, and worse neurological outcome. (25,58,60,61,62) Once initial resuscitation measures have been completed, diagnostic evaluation with a CT scan is indicated, along with a complete physical and neurological exam, serum chemistry, hematology, and toxicology screening. (22,23,32,54)

General Supportive Measures

Once the TBI patient is stabilized and diagnostic tests have been completed, several routine, general supportive measures should be undertaken. Central venous catheters, arterial catheters, jugular venous bulb catheter, and an ICP monitoring device should be placed, if indicated. (1,22,23,53) The head of the bed should be elevated to 30 degrees with the patients head stabilized in a neutral position to enable adequate venous drainage and prevent venous outflow obstruction that may increase ICP. (1) Maintenance fluids should be isotonic saline, and the serum sodium and plasma osmolarity should be maintained within the normal range. Euvolemia should continue to be the goal fluid status. Fluid therapy should be utilized to help maintain an adequate MAP above 90 mm Hg if an ICP monitor is not in place, or to a CPP > 70 mm Hg utilizing an ICP monitor. (1,32) If the MAP is low, and the CVP or pulmonary capillary wedge pressure (PCWP) is adequate, vasopressors may be required to increase

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MAP above 90 mm Hg or to achieve a CPP of 70 mm Hg or greater. (1,32,54)

Serum glucose should be maintained at 4-7 mmol/L as data suggests that hyperglycemia in the setting of ischemia may worsen outcome. Two retrospective reviews have attempted to describe the effect of hyperglycemia on outcome in TBI patients. (63,64) Margulies et al. found that peak glucose levels were inversely related to both GCS on admission and GCS at discharge ($p < 0.001$) in 97 patients with intracranial injuries. (63) However these peak glucose levels may simply reflect the severity of illness and injury in this population as peak glucose was not an independent predictor of outcome in this series. (63) Lam et al. retrospectively reviewed the relationship between serum glucose and outcome in 169 head-injured patients. (64) Patients with lower GCS scores had higher serum glucose concentrations, and patients who remained in a persistent vegetative state or died had significantly higher glucose concentrations than those patients with a good outcome or moderate disability. (64) In the severely injured subgroup (i.e. GCS less than 8), a serum glucose of greater than 11.1 mmol/L was associated with a significantly worse outcome ($p < 0.01$). (64) For these reasons, prevention of hyperglycemia and aggressive control of elevated blood glucose is required. Intravenous fluids (including medication piggybacks) should not contain dextrose, frequent blood glucose monitoring with a glucometer should be performed, and sliding scale insulin may be required to control blood glucose levels.

Oxygen saturation should be maintained above 90% and the PaO₂ should be kept at 60 mm Hg or greater. (1,32,54) Positive end expiratory pressure and inverse ratio ventilation may be required in patients with a pulmonary shunt or oxygenation difficulties, and these modalities may be used safely in TBI patients without compromising ICP. (65,66)

Fever is common in head-injured patients, and increases the body's metabolic rate by 10-13% per degree Celsius. (67,68) Patients with hyperthermia have been shown to have worse neurological outcomes than those patients who remain normothermic. (43) Measurement of rectal temperature alone may significantly underestimate brain tissue temperature by 0.5-2.0°C. (67,68,69) For these reasons, fever prophylaxis with acetaminophen 650 mg every four

hours and/or a cooling blanket should be used to maintain at least normothermia, and possibly hypothermia.

Pain, anxiety, and delirium manifested as agitation along with coughing, respiratory suctioning, and ventilator asynchrony can cause increases in cerebral oxygen consumption and ICP. (10) Thus opioid analgesics, sedatives, and neuromuscular blocking agents may be required. There have been no large studies comparing the effects of sedative agents on outcome in patients with severe head injury. (1,70) Thus, the use of analgesic, and sedative agents should be titrated based on cerebral hemodynamic and oxygenation goals (ICP, CPP, and CERO₂) or by using sedation scales validated in critically-ill patients. (71,72,73) Although opioids have been associated with increases in ICP, several studies have refuted this effect, even with newer, synthetic opioids. (74,75) Until definitive evidence is available, opioids may be used in TBI patients, and ICP should be followed for possible drug-related increases. Tipps et al. recently reported a small case series in which the newer synthetic opioid, remifentanyl was evaluated in the neurological intensive care unit. (76) These investigators found that the ultra-short duration of action of remifentanyl facilitated frequent neurological examinations and no patient experienced deleterious hemodynamic or neurological effects from the use of this drug. (76) Propofol is a sedative-hypnotic agent formulated in a 1% solution in a 10% intralipid carrier. Propofol causes dose-dependent decreases in CMRO₂, CBF, ICP, MAP, and CPP. (77) The advantage of this drug is that it can be titrated easily and patients can be awoken quickly to enable neurological evaluation; however, it does not possess any analgesic properties. A recent pilot, prospective, randomized, double-blind trial compared morphine alone to morphine plus propofol in 42 patients with severe head injury. (77) The use of neuromuscular blocking agents, benzodiazepines, pentobarbital, and CSF drainage was less in the propofol group, and the use of vasopressors was higher in the propofol group due to hypotension. (77) Mortality and neurological outcome was no different between the groups. (77) Until there has been a clinically significant advantage proven with propofol, other sedative agents can be used. If propofol is used, MAP should be monitored closely to ensure CPP is not compromised. Neuromuscular blocking agents may be required in TBI patients; however, they should not be routinely used. A

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prospective, randomized trial of 514 severely head injured patients examining the effects of prophylactic neuromuscular blockade showed that the intervention group had a longer intensive care unit stay, a higher incidence of pneumonia, and a trend toward more frequent sepsis. (78) Complications of neuromuscular blockade including prolonged paralysis and prolonged weakness mandate that these agents be reserved. General measures are used along with specific therapeutic modalities to keep ICP less than 20 mm Hg, maintain CPP at 70 mm Hg or greater, and CERO2 below 40%.

Specific Treatment Modalities

Various specific therapeutic modalities studied in the management of TBI patients have focused on preventing or treating increases in ICP by reducing cerebral blood volume, CSF volume, or brain volume as per the Monroe-Kellie doctrine. (14,15) Lowering ICP or raising MAP will increase CPP. Other therapies have focused on reducing CMRO2 or increasing CDO2 to improve cerebral oxygenation and maintain CERO2 below 40%. Specific therapies include CSF drainage, hyperventilation, mannitol, barbiturate-induced coma, and seizure prophylaxis.

CSF Drainage

The BTF Guidelines recommend ventricular catheters as the ICP monitoring method of choice because of their accuracy, ability to be recalibrated, and because of their ability to drain CSF to acutely lower ICP. (1) Although CSF drainage is recommended as one of the first methods to acutely lower ICP, its effectiveness has never been studied in a randomized clinical trial. (79)

Diuretics

Mannitol has been used to treat suspected or proven increases in ICP in TBI patients. The BTF Guidelines state that the benefits of this drug are assumed to be related to an immediate plasma-expanding effect that reduces the hematocrit, reduces blood viscosity, increases cerebral blood flow, and increases CDO2. This may explain why mannitol reduces ICP within minutes, and why its effects appear more pronounced in patients with low CPP (less than 70 mm Hg).

Secondly, mannitol is thought to establish an osmotic gradient between plasma and brain cells and reducing cerebral edema and ICP by drawing water across an intact blood-brain barrier from the brain into the vascular compartment. (1,12)

Mannitol can be administered at 0.25-1.0 g/kg IV q4h, with an onset of action of several minutes, a peak effect between 20-40 minutes and a variable duration of action. (80) Mannitol administration has been associated with several neurological and systemic adverse effects. Mannitol can worsen vasogenic cerebral edema by passing across an opened blood-brain barrier and causing a reverse osmotic shift to draw water into brain cells, worsen cerebral edema, and paradoxically increase ICP. (81) Although there are no published randomized controlled trials that have compared different modes of administration (bolus versus infusion) or different doses, preliminary data suggests that the accumulation of mannitol in the brain is most marked when mannitol is in circulation for long periods, as occurs with continuous infusions. (1) Other potential adverse effects associated with mannitol administration may be acute congestive heart failure and pulmonary edema, hyperosmolar dehydration and hypotension with prolonged administration, hyponatremia, hypokalemia, acute renal failure when serum osmolality exceeds 320 mOsm/kg, and potential rebound increases in ICP after discontinuation of prolonged therapy. (80)

The effect of mannitol on neurological outcome and mortality has been studied in three well-designed randomized controlled trials, and has been subjected to meta-analysis. A prospective, randomized, double-blind trial by Sayre et al. compared pre-hospital administration of 5 mL/kg of 20% mannitol over 5 minutes compared to 5 mL/kg of normal saline in 41 patients with moderate to severe head injuries. (82) No data were provided for ICP, or disability, but relative risk (RR) for death at 2 hours was 1.75 (95% CI 0.48 - 6.38). (82) This study failed to show a benefit from mannitol, and also failed to exclude a harmful effect on outcome. (82) Smith et al. conducted a prospective, randomized, double-blind trial comparing the administration of ICP-directed and empiric mannitol therapy in 77 patients with severe head injuries. (83) This study also failed to show a benefit of mannitol therapy with a RR of death at one year of 0.83 (95% CI 0.47-1.46). (83) Schwartz et al. conducted a prospective, randomized, single-blind

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trial comparing 1 g/kg of 20% mannitol plus additional boluses versus a load and continuous infusion of pentobarbital in 59 patients with severe head injuries and raised ICP for less than 15 minutes. (84) Again, this trial failed to show a beneficial effect of mannitol on outcome with a RR of death of 0.85 (95% CI 0.52-1.38). (84)

A Cochrane Collaboration meta analysis confirmed that there are insufficient data to preclude either a harmful or beneficial effect of mannitol on mortality. (85) Thus, despite acute reductions in ICP and improvements in CBF, mannitol has not been shown to improve neurological outcome or reduce mortality. Thus the therapeutic goals of therapy for mannitol should be to optimize control of ICP, CPP, and CERO2. The BTF Guidelines recommend mannitol for treatment of elevated ICP in bolus doses of 0.25-1.0 g/kg body weight. (1) Mannitol can be administered to patients without ICP monitoring if there are signs of transtentorial herniation or progressive neurological deterioration not attributable to systemic pathology. (1) Serum osmolality should be kept below 320 mOsm/kg and adequate fluid replacement should be given to maintain euvolemia. (1)

Furosemide is a loop diuretic that has also been shown to be effective in reducing ICP, but to a lesser extent than mannitol. (86) Unlike mannitol, furosemide will decrease production of CSF. (87) When used in combination with mannitol, furosemide (0.1-1 mg/kg) enhances the degree and duration of ICP reduction and it decreases the risk of rebound ICP elevation. (88) A concern associated with the routine use of furosemide is the potential of inducing massive diuresis that would result in depletion of the intravascular volume and electrolytes. Therefore this agent should be reserved to those patients who do not have a satisfactory response to mannitol.

Hyperventilation

Hyperventilation (HV) has been widely used in the treatment and prevention of raised ICP following TBI because it is simple, and rapidly reduces ICP. (1) Two recent surveys published in 1995 and 1996 respectively have shown that HV was used in 83% of American Centres, and 100% of United Kingdom Centres. (89,90) A recently published survey of American Centre neurosurgeons suggests that the use of prophylactic HV

has dropped from 83% in 1991 to 36% in 1997. (91) The use of HV may be dropping due to concerns highlighted in the BTF Guidelines that outline potential drawbacks of HV and summarize the results of several clinical trials re-examining HV therapy. (1) Hyperventilation reduces ICP by causing cerebral vasoconstriction, with a subsequent reduction in CBF and CBV. (1) A potential drawback of HV is that although it may successfully control ICP, it may reduce CBF to ischemic levels. This can be seen during jugular venous bulb monitoring as a drop in SjvO₂, and rise in CERO₂. (10) Under conditions of "luxury perfusion" short-term HV could control acute increases in ICP, without adversely affected cerebral oxygenation. However, in situations of early brain injury (less than 6 hours) during "oligemic cerebral hypoxemia" when CBF is already uncoupled and insufficient to meet CMRO₂, further reductions induced by HV would be expected to further reduce CBF, induce cerebral ischemia, and potentially worsen secondary injury. (10,17,47) For these reasons, the practice of HV is under reassessment.

Muizelaar et al. performed a prospective, randomized, unblinded trial comparing normocapnia, HV, and HV plus tromethamine (THAM) buffering over 5 days in 77 patients with severe TBI and assessed neurological outcome at 3, 6, and 12 months. (46) Overall, the study failed to show a benefit of HV or HV plus THAM on combined death or severe disability (RR = 1.14 (95% CI 0.82-1.58), RR = 0.87 (95% CI 0.58-1.28)) or mortality (RR = 0.73 (95% CI 0.36-1.49), RR = 0.89 (95% CI 0.47-1.72)) respectively. (46) Interestingly, in the subgroup with a motor GCS score of 4-5, fewer patients had a favorable outcome (good or moderately disabled) in the HV groups at 3 and 6 months (p<0.05). (46) This difference did not remain significant after 12 months, likely due to a lack of statistical power. (1,46) Based on the results of this trial, the BTF has re-evaluated the practice of HV therapy. (1) The current BTF Guidelines recommend that in the absence of increased ICP, chronic prolonged HV therapy (PaCO₂ less than 25 mm Hg) should be avoided after severe TBI. (1) The use of prophylactic HV therapy (PaCO₂ less than 35 mm Hg) during the first 24 hours after severe TBI should be avoided because it can compromise CPP when CBF is reduced. (1) HV therapy is most appropriately reserved for acute neurological deterioration associated with elevated ICP, or for more prolonged periods when elevated ICP is refractory to other

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treatments. (1) The guidelines recommend that jugular venous saturation monitoring be used to monitor for cerebral ischemia if short-term HV resulting in a PaCO₂ of less than 30 mm Hg is required to acutely reduce elevated ICP. (1)

A recent study has been published that involved an evaluation of the effects of early moderate (PaCO₂ of 30 ± 2 mm Hg) hyperventilation in nine patients within 12 hours of injury. (92) In this study the investigators measured CBF, CMRO₂, CBV, cerebral venous oxygen content (CvO₂), and CERO₂. These investigators found that during hyperventilation, global CBF decreased, CBV fell, CERO₂ rose, CvO₂ fell, and CMRO₂ remained changed. They concluded that brief, moderate hyperventilation soon after injury does not alter cerebral metabolism and is unlikely to harm the patient. However, further study is necessary to evaluate focal changes and the effects in patients with elevated ICP. (92)

Barbiturates

If CSF drainage, mannitol, and HV fail to control an elevated ICP and improve cerebral oxygenation, high-dose barbiturate therapy has been used as a last pharmacologic resort prior to emergency non-dominant temporal lobectomy with or without craniectomy. (1,22,23) Others have used barbiturate therapy prophylactically in an attempt to improve outcome. Barbiturates reduce CMRO₂, thus reducing cerebral metabolic demands, CBF, CBV, and ultimately ICP to enhance global cerebral perfusion and improve cerebral oxygenation. (1,93) At least one trial suggests that normal metabolic coupling between CMRO₂ and CBF is necessary for barbiturates to be effective. (94) Barbiturate therapy has also been associated with important complications such as infection, hypothermia, and hypotension (which may reduce CPP and offset any beneficial effects from ICP reduction). (93) Despite these controversies, surveys published in 1995 and 1996 respectively have shown that barbiturates were used in 56% of UK intensive care units and 33% of American intensive care units at that time. (89,90) Since 1974, case series data have suggested beneficial effects of barbiturate therapy on raised ICP. (95,96,97,98) These preliminary data suggest that ICP can be adequately controlled with barbiturates, neurological outcome can be improved, and mortality can be reduced.

Four well designed clinical trials have been published that involved the evaluation of barbiturate therapy for the management of head injury. (29,84,99,100,101) Two studies assessed prophylactic administration of barbiturates or their use in initial therapy for ICP elevations. Ward et al. performed a randomized, controlled trial of pentobarbital versus no pentobarbital in 53 head-injured patients with acute intradural hematoma or whose best motor response was abnormal flexion or extension. (99) Although the mean ICP and temperature were lower in the barbiturate group, hypotension (SBP less than 80 mm Hg) was significantly more common in the treated patients (54% versus 7%, $p < 0.05$), and may have reduced CPP. (99) There was no significant difference in 1-year Glasgow Outcome Scale (GOS) score between the groups. (99) Schwartz et al. conducted a prospective, randomized, single-blind trial comparing a load and continuous infusion of pentobarbital to 1 g/kg of 20% mannitol plus additional boluses in 59 patients with severe head injuries and raised ICP for greater than 15 minutes. (84) Pentobarbital was less effective than mannitol at controlling ICP with 68% of pentobarbital patients and 39% of mannitol patients requiring a second drug for treatment of ICP (RR = 1.75 95% CI 1.05-2.92). (84) This study failed to show a difference in mortality between the two groups (RR = 1.21 95% CI 0.75 - 1.94). (84) Levy et al. performed a randomized, controlled trial in head injury patients comparing pentobarbital and etomidate for control of raised ICP. (100) This trial was stopped after 7 patients were enrolled due to patients in the etomidate group developing renal failure. (100) The final trial is a prospective, randomized, double-blind multicentre trial published by Eisenberg et al. in 1988. (29) In this study, 73 patients with severe head injury (GCS 4-8) and intractable elevations in ICP were randomized to receive high dose pentobarbital 10 mg/kg over 30 minutes, followed by 5 mg/kg/h for 3 hours, and a 1 mg/kg/h infusion versus conventional therapy (no pentobarbital). (29) Serum pentobarbital levels of 30-40 mg/L were attempted. The primary outcome in this trial was controlled ICP less than 20 mm Hg. A smaller proportion of patients in the pentobarbital group had uncontrolled ICP (68% vs. 83%, $p = 0.22$), although this was not statistically significant. (29) The authors reported that the likelihood of survival in barbiturate responders was 92% at one month compared with 17% for non-responders. (29) Unfortunately the design of this

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study and others did not enable a conclusive determination on the effect of barbiturates on death or adverse neurological outcome. (1, 29)

A recent Cochrane Collaboration meta analysis examined the effects of barbiturates on outcome after TBI found no effect on mortality or morbidity (Table 4). (101) These data concur with an earlier meta analysis by Roberts et al. which also found no beneficial effect of barbiturates (Table 4). (102) Thus, all the data to this point have failed to show a beneficial effect on outcome with barbiturates in head injury. Unfortunately, the risk of hypotension was significantly higher than no therapy and translated to a fall in BP in 1 of every 4 patients treated. (101,102) Thus, if barbiturates are to be used for refractory increases in ICP, the pentobarbital regimen by Eisenberg should be followed. (1) According to the BTF Guidelines, barbiturate therapy may be considered in hemodynamically stable salvageable severe TBI patients with elevated ICP refractory to maximal medical and surgical therapy. (1) The pentobarbital infusion should be titrated to pentobarbital levels of 30-40 mg/L or preferably burst suppression on EEG. (93,103). It is important to monitor for hypotension, and vasopressor agents should be readily available during the loading period to support MAP and maintain a CPP greater than 70 mm Hg. (93)

Anticonvulsant Prophylaxis

The incidence of generalized seizures in patients suffering a head injury is 5%-10%. (10) The incidence of post-traumatic seizures (PTS) is higher in patients with a GCS less than 10, cortical contusion, depressed skull fracture, subdural hematoma, epidural hematoma, intracerebral hematoma or penetrating head wound. (1) PTS have been classified into early (occurring within 7 days of injury) or late (occurring after 7 days following injury) seizures. (1) In the convalescent period following TBI, seizures may exacerbate secondary injury by increasing ICP, increasing CMRO₂, CBF, CBV, lowering MAP, and potentially lowering CPP to worsen cerebral oxygenation. (10,11) Seizures may also lead to complications such as exacerbation of head injury, aspiration, nosocomial pneumonia, and a generally poorer overall outcome. For these reasons, and based on positive results from early retrospective trials,

seizure prophylaxis was commonly prescribed by U.S. neurosurgeons for head-injured patients in the 1970s. (104) However, potential drawbacks of routine anticonvulsant prophylaxis can include dose-related CNS and gastrointestinal adverse effects, and idiosyncratic effects ranging from a mild rash to Steven-Johnson's Syndrome. (1)

One of the earliest randomized, controlled trials conducted to study the effect of phenytoin prophylaxis on the development of early and late PTS prophylaxis was performed by Young et al. in 1983. (105) In this study, 244 patients with head injuries were randomized to receive phenytoin or placebo and followed for two years. Patients received an 11 mg/kg IV loading dose, followed by IM or oral dosing guided by daily plasma phenytoin sampling in an attempt to achieve target plasma phenytoin levels of 40-80 umol/L. (105) According to the authors, there was no apparent difference in the incidence of early or late seizures between the treatment (3.7% and 12.4%) and the control (3.7% and 10.8%) groups. (1,105) This lack of apparent difference may be explained by the low incidence of seizures in the placebo group, which reduced the power of the trial to detect a difference. (1,105) During the early phase of the study, serum concentrations were obtained every 24 hours, and 78% of patients had plasma phenytoin concentrations of at least 40 umol/L. (105) Moreover, none of the patients with phenytoin plasma concentrations above 48 umol/L experienced a seizure. (105)

In 1990, Temkin et al. performed the largest prospective, randomized, double blind, placebo-controlled trial evaluating the effectiveness of phenytoin for the prevention of PTS in patients with severe head injuries. (106) In this study, 404 patients were randomized to receive a phenytoin 20 mg/kg IV loading dose followed by IV, oral, or nasogastric maintenance dosing that was guided by thrice weekly plasma phenytoin concentrations in the ICU, weekly on the ward, and at 1, 3, 6, 9, and 12 months during the 24 months follow-up. The daily doses varied considerably throughout the study and ranged from 200-1200 mg/d IV or orally, and up to 2600 mg/d given via the nasogastric route. The target phenytoin concentrations were 40-80 umol/L (total) or 3-6 umol/L (free). The incidence of early PTS was found to be significantly lower in the treatment group (3.6% (95% CI 2.3-4.9) versus 14.2% (95% CI 11.6-16.8), (p<0.001), RR = 0.27 (95% CI 0.12 to 0.62), number

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needed to treat (NNT) 10 (95% CI 8-18)) to prevent one early seizure. No significant reduction in late PTS between groups was observed. Eighty-one percent of patients had attained free phenytoin plasma concentrations between 3.0-7.9 mmol/L following the loading dose, while at one week only 45% of measured plasma concentrations were within the same range. At the scheduled outpatient visits starting at one month, levels were at least therapeutic in 70% of patients. The drop in plasma phenytoin concentrations may have been due to early under-dosing and/or previously described pharmacokinetic alterations in severe TBI patients affecting protein binding and/or phenytoin metabolism. (107,108) There was a significantly higher incidence of rashes causing drug discontinuation in the phenytoin group (8.2 % versus 2.0%, ($p < 0.01$), number needed to harm (NNH) of 17)). Using the initial Temkin data, for every 1000 patients treated with phenytoin, 111 seizures would be prevented and 62 patients would be expected to discontinue therapy as a result of the development of a rash. The Temkin trial had greater statistical power than the Young trial and likely showed a benefit because the population was at higher risk for seizures than those in the Young trial. The Temkin trial data have been re-analyzed to investigate the incidence of adverse effects during the first 2 weeks of therapy. (109) Based upon this new analysis, the overall incidence of adverse effects was found to be similar in the two groups (9% for phenytoin vs. 6% for placebo, $p = 0.52$) as was the incidence of rash during the first week (0.6% vs. 0%, $p = 1.0$). (109) Given that there is no difference in adverse effects between phenytoin and placebo, decisions on the use of 7 days of phenytoin prophylaxis should be made based on the clinical significance of the effects on seizure prevention and overall neurological outcome.

A more recent prospective, randomized, double blind trial by Temkin et al. involved a comparison of valproic acid with phenytoin for the prevention of early and late PTS in 379 patients with head injury. (110) Patients were enrolled if they had an immediate PTS, depressed skull fracture, penetrating brain injury or there was CT evidence of a cortical contusion, subdural, epidural, or an intracerebral hematoma. Patients were assigned to receive phenytoin therapy for 7 days, valproic acid therapy for 30 days, or valproic acid for 180 days. The incidence of early seizures was low and did not differ between the phenytoin and pooled valproic acid groups (1.5% versus

4.5%, $p = 0.14$), $RR = 2.9$ (95% CI 0.7 - 13.3)). Due to the high upper confidence interval, the study did not have the power to exclude a potentially clinically significant inferior effect of valproic acid. The incidence of late seizures was not different between the groups, although there was a trend toward a higher mortality rate in patients receiving valproic acid vs. phenytoin (13.4% vs. 7.2%, $p = 0.07$, $RR = 2.0$, 95% CI 0.9 - 4.1). For these reasons, valproic acid cannot be routinely recommended for the prevention of PTS until more data are available.

The Cochrane Collaboration group has published a recent meta analysis identifying 10 eligible randomized controlled trials involving 2,036 patients who were randomized to anticonvulsant therapy or placebo for PTS prophylaxis. (111) Data on early seizure frequency available from 4 published trials (890 patients) suggested that anticonvulsant agents reduced the incidence of early PTS but not late PTS, and failed to show a reduction in corresponding mortality (Table 4). Neither phenytoin prophylaxis nor carbamazepine prophylaxis resulted in a reduction in death and neurological disability for treated versus untreated patients (Table 4). Based on the trend towards an increase in death and neurological disability in this meta analysis, carbamazepine may actually be expected to increase death or neurological disability; however, the clinical significance of this finding is difficult to determine (Table 4). The analysis failed to rule out a clinically significant increase in skin rashes. Thus, based on the current data, the prophylactic use of anticonvulsants to prevent late PTS is not currently recommended in the BTF Guidelines and Practice Parameters by the Brain Injury Special Interest Group of the Academy of Physical Medicine and Rehabilitation. (1,112) Phenytoin is considered acceptable therapy for the prevention of early PTS; however, the current data do not support a reduction in overall mortality or death and neurological disability. (1,111) If phenytoin is used to prevent early PTS, a loading dose of 20 mg/kg, followed by an aggressive maintenance dose of 5-7 mg/kg/d (ideal body weight) should be used during the first week of therapy to attain target plasma phenytoin concentrations of 40-80 $\mu\text{mol/L}$ (total) or 4-8 $\mu\text{mol/L}$ (free) in this hypermetabolic patient population. (107,108)

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Experimental Therapies for TBI

Induced Hypothermia

Fever is common in TBI patients, increases the body's metabolic rate, and is associated with worse neurological outcomes in TBI patients. For these reasons, induced therapeutic hypothermia has been used experimentally and in clinical trials as a method to reduce ICP and CMRO₂ in an attempt to improve neurological outcome after TBI. (1) The mechanism of protection conferred by induced hypothermia is unknown. Originally it was thought to be due to a reduction in CMRO₂ (113); however, hypothermia may also influence the excessive post-traumatic release of excitatory neurotransmitters (114), and attenuate opening of the blood-brain barrier. (115,116) Potential risks of induced hypothermia include pneumonia, sepsis, coagulation abnormalities, myocardial ischemia and atrial fibrillation. (116,117)

A reduction in body temperature from 37°C to 32°C reduces CMRO₂ by approximately 10%. (10) A preliminary prospective trial in severe head injury revealed that mild hyperthermia to 33.5-34.5°C significantly reduced ICP and increased CPP in patients refractory to high-dose barbiturate therapy. (118) In another study involving 33 severe head injury patients with refractory increases in ICP who received deferred moderate therapeutic hypothermia to 32-33°C, this body temperature reduction was found to reduce ICP and CBF by 40 % ($p < 0.004$) and 26 % ($p < 0.021$), respectively. The survival rate was also found to be higher in the treatment group ($p < 0.05$). (40) More recently, Marion et al. completed the largest prospective, randomized, double blind trial in 82 severely head-injured patients. (119) Body temperatures were reduced to 32-33°C approximately 10 hours after their injury, and these temperatures were maintained for 24 hours. Among patients with a GCS of 5-7, hypothermia was found to be less likely associated with a poor outcome of death, vegetative state, or severe disability (GOS of 1-3) compared to normothermia at 3 months (63% versus 83%, adjusted RR = 0.2 (95% CI 0.1-0.9), NNT of 5), and 6 months [45% versus 67%, adjusted RR = 0.2 (95% CI 0.1-0.9), NNT of 5], but not at 12 months (38% versus 62%, adjusted RR = 0.3 (95% CI 0.1-1.0)).

To determine the impact of induced hypothermia on mortality and neurological outcome, the Cochrane Collaboration conducted a meta analysis of 8 randomized controlled trials. (41,116,118,119,120,121,122,123,124) Trials were stratified into two groups: those that looked at active immediate hypothermia or deferred hypothermia. (116) Meta analysis failed to show a benefit of active, immediate hypothermia versus normothermia on mortality; however, a 61% reduction in the risk of death or severe disability was observed (Table 4). This translates in to a NNT of 4 (3-13) to prevent one patient from dying or being disabled. This apparent clinical benefit should be interpreted cautiously as the result may be due to publication bias. Only one trial of 33 patients involved an assessment of deferred hypothermia and reported deaths and GOS at 6 months. (118) This trial failed to show a significant difference in the risk of death (50% versus 82%, OR = 0.21 (95% CI 0.04-1.5)) or death or severe disability (63% versus 94%, OR = 0.10 (95%CI 0.01-1.00)). (116,118) Larger trials are necessary to confirm or refute the effect of induced or deferred hypothermia on long-term outcomes. All of the above trials involved reducing body temperatures to a range of 30-34.5°C for a maximum of 48 hours.

There are no published data to suggest a target cooling temperature, or ideal duration of cooling. However, Bernard et al. recently reported that a moderate hypothermia of 30-33°C for 8 days provided a satisfactory neurological outcome in 20 (47%) of 43 severely head-injured patients. (125) In this study there was a high incidence of nosocomial pneumonia (45%) and hypokalemia on cooling induction, and a decrease in total WBC and platelet counts over 10 days. (125) Another recent trial evaluated mild hypothermia (34°C) for 48 hours involving 16 severely head-injured patients in whom ICP was maintained below 20 mm Hg with conventional therapies. (126) There was no difference in neurological outcome and the authors concluded that mild hypothermia does not convey any benefit over normothermia for those patients with ICP maintained at less than 20 mm Hg using conventional therapies. (126) The potential drawbacks of induced hypothermia can include the induction of shivering which can increase CMRO₂, CERO₂, ICP, and lower CPP. To overcome this problem patients often require pharmacological paralysis with its inherent risks of prolonged paralysis and weakness. Controversies surrounding induced

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hypothermia will hopefully be resolved when a National Acute Brain Injury Study of hypothermia is published later this year. This study involves an examination of the effect of hypothermia (32-33°C) for 48 hours on GOS at 6 months in 392 severely brain-injured patients. (127)

Corticosteroids

Our ability to draw conclusions from existing studies of corticosteroids in TBI has been limited due to poor study design including a lack of control groups and blinding, inadequate sample sizes, and drug dosing inconsistencies. (128) Although corticosteroids are effective in reducing cerebral edema in patients with structural brain damage, these agents have not been shown to ameliorate increased ICP nor improve long-term outcomes. This has been thought to be due to the inability of steroids to prevent early cytotoxic edema and may also be related to corticosteroid-induced hyperglycemia, increased infection rates and/or gastrointestinal bleeding. (1,128)

Two meta analyses involving an assessment of corticosteroid trials have been reported. (128,129) In one analysis, 19 trials involving corticosteroid use for 2295 TBI patients were reviewed. (129) Mortality data extracted from 16 trials failed to show benefit on mortality, and data from 9 trials failed to show benefit on the aggregate endpoint of death or disability (Table 4). Another meta analysis that found similar results included many of the same trials, but had more stringent exclusion criteria. (128) Mortality data from 13 randomized trials involving 2073 patients failed to show benefit on mortality, and data from 10 trials failed to show benefit on the aggregate endpoint of death or disability. Both analyses failed to show a difference in infection rates and gastrointestinal bleeding between those who received corticosteroid and those who did not. It is important that although these data fail to show a significant benefit of corticosteroids on outcome, they also fail to exclude a potentially clinically significant absolute mortality reduction of up to 5.7%. (128) Even pooled together, the current trials are too small to support or refute a clinically important benefit from corticosteroids. Although a very large, multicentre trial would be required to solve this clinical dilemma, such a trial may be justified based on the clinical impact of the problem and the widely practicable treatment. (128)

The current BTF Guidelines state, however, that corticosteroids are not recommended in TBI patients to lower ICP or improve outcome. (1) Despite that recommendation and the lack of evidence to support their use, the recent survey from Marion et al. suggests that 19% of U.S. Neurosurgeons would use corticosteroids in this setting. (91) The routine use of corticosteroids in TBI patients should be avoided until supported by clinical trial evidence.

Indomethacin

Indomethacin is a non-steroidal anti-inflammatory agent with unique effects on cerebral blood flow physiology that may be of benefit in reducing elevated ICP in TBI patients. Data from animal models and randomized, controlled studies with pre-term infants have shown that IV indomethacin produces rapid, significant reductions in cerebral blood flow (CBF). (47) Controlled studies of IV indomethacin in normal volunteers show a reduction in CBF from 26-40%. (47) Case series involving severe TBI patients suggest that indomethacin IV boluses of 30-50 mg reduce ICP by 37-52%, reduce CBF by 22-26%, with a modest 14% increase in cerebral perfusion pressure (CPP). (47) The onset of effects is almost immediate, and peaks in 1-5 minutes. The duration of ICP control is at least 4 hours and may be as long as 30 hours with a continuous infusion (CI). (47) ICP returns to baseline levels after the infusion is stopped. (47) No significant adverse effects have been reported but short-term changes in sensitive physiologic indicators of cerebral ischemia are of potential concern. Using indomethacin for ICP control may be potentially harmful to patients who already have normal or high CEO2 or impaired autoregulation. In this subgroup, indomethacin may decrease CBF to ischemic levels that may not be overcome by a subsequent increase in CEO2. Indomethacin may also cause coronary ischemia in patients with ischemic heart disease, especially during anemia, hypoxemia, hypotension, systemic shunting, or impaired CEO2. For these reasons, some have suggested that indomethacin should not be used in patients with low SjvO2 (less than 60 %), low CMRO2 (less than 40 mL/100g/min), signs or symptoms of cerebral vasospasm, cardiac ischemia, renal failure, or bleeding ulcer. (130)

Important efficacy and safety issues regarding indomethacin use in TBI patients must still be

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addressed before it can be generally recommended for ICP control. Normal volunteer dose-response studies with IV bolus, CI, and PR dosing will characterize the pharmacodynamics of indomethacin on normal cerebral physiology. The effects of indomethacin on cerebral oxygenation in patients without luxury perfusion or those receiving therapeutic hyperventilation need to be determined. The effect of indomethacin on ICP and subsequent cerebral oxygenation must be studied, and the influence of these effects should be documented using functional neurological outcome scales. Thus, despite encouraging preliminary results, IV indomethacin should only be considered an experimental treatment for control of refractory ICP in TBI patients. Larger, well-designed randomized trials in TBI patients will provide more efficacy and safety data and delineate the effects of indomethacin alone or in combination with other proven, effective, or experimental therapies. Once these concerns have been addressed, larger outcome studies will ultimately be needed to determine the role of indomethacin for ICP control in TBI patients.

Neuroprotection

As mentioned previously, the secondary injury cascade is a complex biochemical loop that results in propagation of neurological injury. (Figure 1) Laboratory studies with numerous agents identified potential therapeutic targets for neuroprotection following TBI. (131) However, the positive effects shown in animal models have not been replicated in clinical trials. Some of these clinical investigations progressed to completion; however, many were prematurely halted due to interim "futility analyses" or due to concerns with safety. This has led to many theories regarding why these discrepancies occur including a lack of sensitivity in outcome measures, improper timing of therapeutic intervention, an inability to translate injury mechanisms in animals to human head injuries, poor brain penetration of drugs or inadequate doses used; and insufficient safety and tolerability investigation of the agent in question prior to the study. (131) There are many questions that still need to be answered including refining our understanding of the pathophysiology of TBI and the timing of these events. This section is devoted to a discussion of neuroprotective agents both past and present.

Increases in intraneuronal calcium seen with TBI initiates a cascade of biochemical events that can eventually result in cell lysis and death. Calcium-channel blockers in experimental models attenuated the increase in intracellular calcium concentration and thereby arresting neurological damage. (18) Nimodipine is a "cerebroselective" dihydropyridine calcium channel blocker that is approved by the Food and Drug administration to decrease the neurological morbidity following aneurysmal subarachnoid hemorrhage (SAH). This agent blocks the L-type calcium channel. The postsynaptic L-type channel remains open during depolarization to allow for excessive calcium accumulation. Blocking this channel may prevent the calcium buildup and it may have vasodilatory effects on cerebral vascular smooth muscle. Two large randomized, controlled trials have been performed to study the effect of nimodipine on the outcome of severe head injury, HIT I and HIT II. (132,133) Both trials showed a modest and an insignificant increase in the proportion of favorable outcomes in patients treated with nimodipine. A reanalysis of pooled data from both the HIT I and HIT II trials using IV nimodipine found that the overall benefit of treating unselected head injured patients with nimodipine is unlikely to be clinically relevant. (134) However a subgroup analysis of the HIT II trial suggested that there could be a possible protective effect of nimodipine in patients with traumatic SAH. (133) Another prospective, double-blind trial conducted in Germany randomized 123 TBI patients with a traumatic SAH to nimodipine (2 mg/h) or a matched placebo intravenously for 7 to 10 days, followed by oral treatment (360 mg daily) until day 21. (135) Patients treated with nimodipine had a significantly less unfavorable outcome (death, vegetative survival, or severe disability) at 6 months than placebo-treated patients (25% vs. 46%, $p=0.02$, OR 0.39, 95% CI 0.18-0.86). Therefore, due to these promising preliminary results, nimodipine is currently being investigated in a Phase III trial in patients with traumatic SAH with GCS 4-15.

Activation of the presynaptic N-type calcium channel in the nerve terminals is the leading cause of excitatory amino acid release during ischemia. Therefore, blockade of this channel might reduce this excitotoxic process. The omega-conopeptide SNX-111, obtained from a carnivorous marine snail, is a potent antagonist of the voltage-gated N-type calcium

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channel and has demonstrated significant neuroprotective effects against neuronal injury. (136,137,138) However, the limiting adverse effect of this agent was hypotension, which could possibly lower CPP and affect outcome. This trial was halted due to a futility analysis indicating that the drug could not be safely used outside a controlled clinical trial setting. Following injury, release or formation of highly reactive free radicals may produce secondary damage to cellular membranes. This type of injury occurs through a process called lipid peroxidation, which is accelerated in the presence of free reactive iron. (18) Endogenous defense mechanisms and antioxidants were identified that scavenged free radicals. These systems include; superoxide dismutase (SOD), tocopherols, ascorbic acid, and retinoic acid. However, after injury the endogenous levels of these systems are depleted which permits progressive destruction of the cellular membrane. In the laboratory, scavenging of the superoxide anion SOD or polyethylene glycol (PEG)-conjugated SOD (PEG-SOD) has been shown to be beneficial following TBI. (139) A Phase II study included 104 patients randomly assigned to receive either placebo or PEG-SOD (2000, 5000, or 10,000 U/kg) intravenously as a bolus, an average of 4 hours after injury. At 3 months, 44% of patients in the placebo group were vegetative or had died, while only 20% of patients in the group receiving PEG-SOD were in these outcome categories ($p < 0.03$); similarly at 6 months, the same outcomes were 36% and 21%, respectively ($p = 0.04$). (140) From this study it appeared that PEG-SOD was a promising therapy. However, in a follow-up prospective, randomized, double-blind, placebo-controlled multicentre study of 463 patients treated within 8 hours of injury, no statistically significant difference in neurological outcome or mortality was observed between patients treated with PEG-SOD and those receiving placebo. (141) Therefore the use of PEG-SOD in clinical practice was abandoned.

A novel group of compounds, the 21-aminosteroids ("lazaroids"), also emerged as potent inhibitors of oxygen free radical-induced, iron-catalyzed lipid peroxidation. One of these, tirilazad mesylate (U-74006F), was selected for clinical investigation in various models of neurological injury. Preclinical models found that tirilazad improved neurological outcome when given between 5 minutes and 3 hours after injury. (142,143) The Phase III trial of tirilazad evaluated a cohort of 1120 head-injured patients.

(144) Six-month outcomes for the tirilazad and placebo-treated groups for the Glasgow Outcome Scale categories of both good recovery and death showed no significant difference. However, subgroup analysis suggested that tirilazad mesylate may be effective in reducing mortality rates in males suffering from severe head injury with accompanying traumatic SAH. The investigators also described problems with imbalances in prognostic variables such as pretreatment hypotension, pretreatment hypoxia, and the incidence of epidural hematomas. (144) This study further emphasized the heterogeneous nature of TBI and the need for better randomization strategies to allow for a more homogenous study sample.

Excitotoxic mechanisms due to over-activity of the amino acid neurotransmitters glutamate and aspartate may be responsible for brain damage after injury. Glutamate activates the NMDA receptor that results in failure of the cellular ionic pump. Pharmacological antagonists of excitatory amino acids represent the most highly investigated class of agents following TBI. The competitive NMDA-receptor antagonist, CGS19755 (Selfotel) has been evaluated in the clinical setting with data reported from two phase III clinical trials. (145) A total of 693 TBI patients with a GCS of 4-8 and at least one reactive pupil were randomized to placebo or an intravenous infusion of 5 mg/kg of Selfotel once daily for 4 days. Due to possible increased deaths and serious brain-related adverse effects in the treatment arms of the two head injury trials and in two stroke trials, the Safety and Monitoring Committee stopped the trial prematurely. An interim efficacy analysis also indicated that it would be futile to continue the trial because the likelihood of demonstrating success with the treatment arm was almost nil. In the final analysis there was no statistically significant difference in mortality between the treatment groups. Cerestat (CNS 1102), a noncompetitive NMDA-receptor antagonist has also been evaluated in human TBI and did not show a positive effect. (131) CP-101,606 is a postsynaptic antagonist of the glutamate-mediated NR2B subunit of the NMDA receptor. A safety evaluation of CP-101,606 in patients with moderate or mild TBI or hemorrhagic stroke has been reported. Patients began receiving treatment within 12 hours of brain injury. The drug/placebo was administered by intravenous infusion for up to 70 hours. All the patients tolerated the drug, and there were no clinically significant cardiovascular, psychotropic, or

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hematological complications. (146) This agent is currently in Phase III testing and results are not yet available.

Some of the other agents currently being investigated include cyclosporine and magnesium. Cyclosporine transiently inhibits the opening of the mitochondrial permeability transition pore and maintains calcium homeostasis in isolated mitochondria. (147) Animals who received cyclosporine either 5 minutes before injury or immediately following injury show a significant reduction in the amount of cortical damage 7 days after TBI. (148) Another animal model administered a 20 mg/kg intraperitoneal bolus of cyclosporine or vehicle 15 minutes post injury found that all animals receiving cyclosporine demonstrated a significant reduction in lesion volume. (147) Cyclosporine was also shown to inhibit calcium-induced axonal damage when administered 30 minutes after injuries. (149) These investigations suggest that there is a therapeutic window for the use of drugs targeting mitochondria and energy regulation in traumatic brain injury. (149) However, it is yet to be seen if these positive laboratory results will translate into significant clinical benefit.

Magnesium is another agent now being investigated for its potential neuroprotective properties. An animal model has been used to demonstrate that magnesium plays a role in neuroprotection following severe diffuse traumatic axonal brain injury. Magnesium was shown to significantly improve motor outcome when administered up to 24 hours after injury. As would be expected, early treatments provided the most significant benefit and repeated administration beyond 24 hours post injury did not provide additional effects. (150) Magnesium appears to be promising but needs further evaluation before being tested in clinical trials.

Due to the ongoing high morbidity and mortality associated with conventional treatment of severe TBI, novel therapeutic strategies are being developed. One of these strategies is "Lund Therapy" of posttraumatic brain edema, named after the Lund University Hospital in Sweden. (151) This therapy attempts to prevent cerebral hypoxia while simultaneously counteracting transcapillary filtration. The Lund treatment protocol includes the following: 1) preservation of normal colloidal-absorbing force; 2) reduction in intracapillary

pressure through a reduction in systemic blood pressure by antihypertensive therapy (metoprolol combined with clonidine); and 3) simultaneous, moderate constriction of precapillary resistance vessels with low-dose thiopental and dihydroergotamine. A cohort of 53 consecutive severe TBI patients admitted from 1989-1994 who were treated with Lund Therapy was compared with a historical control group of 38 severe TBI patients treated from 1982-1986. Fewer patients in the Lund Therapy group died (8% vs. 47%, $p < 0.0001$), and the ratio of patients with a favorable outcome was significantly higher in the Lund Therapy group ($p < 0.001$). (151) Due to methodological weaknesses of this study design, these hypothesis-generating results will need to be confirmed in a randomized clinical trial. (151)

The future of pharmacological neuroprotection is unclear at the present time. Several compounds have been tested and none have been shown effective in the clinical setting. The need for clinically effective agents is apparent especially in light of the devastating morbidity and mortality following severe TBI. It is the hope of many clinicians that these previous negative studies have taught us more about this injury and possible ways to plan clinical trials to avoid these same problems in the future.

Summary

TBI causes significant mortality, morbidity, and contributes substantially health care costs. Understanding normal cerebral physiology and altered physiology due to primary and secondary injury is essential to the identification of potentially useful therapies. Unfortunately, many of the specific therapies evaluated to date have not been shown to provide clinically important benefits.

CSF drainage and diuretics have failed to show a benefit on neurological outcome or mortality. Despite acute reductions in ICP and improvements in CBF with mannitol therapy, there are insufficient data to preclude either a harmful or beneficial effect on mortality. Hyperventilation may acutely control ICP; however, it has not been shown to improve outcome, and may worsen outcome if it is used routinely for long periods of time. Barbiturates may also improve surrogate physiologic markers in TBI, but they have

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failed to improve outcome, and are associated with a risk of hypotension in one out of four patients that may adversely affect CPP. Anticonvulsant prophylaxis has been shown to prevent early seizures after TBI, but failed to show a beneficial effect on outcome. Induced hypothermia reduces ICP, CBF, improves CPP, and meta analysis data have suggested that when used for less than 48 hours induced hypothermia is associated with a reduction in death or disability in TBI patients. Controversies regarding induced hypothermia may be resolved when a National Acute Brain Injury Study of hypothermia is published later this year. Meta analyses have failed to show a beneficial effect on mortality or neurological outcome in TBI patients treated with corticosteroids; however, a small but important beneficial effect of corticosteroids cannot be ruled out. Although a large clinical trial evaluating corticosteroids may be warranted, at this point routine corticosteroid therapy cannot be recommended.

Due to the disappointing results with specific therapies for TBI to date, specific experimental therapies and neuroprotective agents will continue to be evaluated. To date, many promising experimental neuroprotective strategies have not been proven beneficial in the clinical setting, but further studies are needed. Studies comparing overall management strategies that include therapies not shown to be harmful would also be beneficial and may enhance the effect size shown in the experimental group. Thus, until more data are available, specific goals of therapy published in TBI guidelines and consensus articles should be followed: 1) controlling ICP less than 20-25 mm Hg; 2) maintaining CPP at or above 70 mm Hg or MAP above 90 mm Hg in the absence of an ICP monitor; 3) optimizing cerebral oxygenation by ensuring normal coupling between CMRO₂ and CBF and maintaining CEO₂ below 42% (CERO₂ less than 40%); (1,32) and 4) preventing and/or treating cerebral and systemic complications of TBI is also essential in these patients.

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Issues in Pharmacotherapy Practice

Community-Acquired Pneumonia - What is the State of the Art?

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Abstract

Community-acquired pneumonia (CAP) is the 6th leading infectious cause of death with an incidence of 12 cases per 1000 population. In the United States, CAP accounts for 40,000-60,000 deaths and 600,000 to 1 million hospitalizations per year. The objective of this article is to review some of the issues and highlight areas of controversy in the management of CAP. *Streptococcus pneumoniae* is the most common cause of CAP, occurring in 20-60% of cases. In 40-60% of CAP cases, a bacterial cause cannot be found, necessitating empiric antibiotic therapy. The prevalence of penicillin-resistant *S. pneumoniae* (PRSP) is increasing and has now become a global concern. The emergence of PRSP has spurred an emphasis on the newer macrolides and the new fluoroquinolones. Issues such as the clinical impact of PRSP, the role of atypical pathogens in CAP and treatment guidelines have resulted in confusion as to what is the "drug of choice" for CAP. Guidelines have been developed to assist clinicians in selecting an antimicrobial agent. The evolving nature of CAP management will continue to stimulate discussion for many years to come.

J Inform Pharmacother 2000;3:336-344.

Introduction

Community-acquired pneumonia (CAP) is the 6th leading infectious cause of death accounting for 40,000-60,000 deaths and 600,000 to 1 million hospitalizations per year in the United States (1). Community-acquired pneumonia is reported to occur in 2.3% of the population with an incidence of 12 cases per 1000 population (2,3). Elderly patients (often with co-morbidities) account for the majority of hospitalizations. The economic impact from CAP is significant; the annual cost of treating patients with CAP is estimated to be \$8 billion (US) (2). Significant research has been devoted to CAP over the past several years resulting in a better understanding of the bacterial etiology, prognosis and risk factors associated with CAP. In addition, the use of management guidelines and the availability of new antimicrobial classes have provided clinicians with many treatment options. Despite these developments, questions pertaining to the management of CAP persist. The objective of this article is to briefly review CAP (definition, etiology, risk factors and prognosis) while highlighting new developments and areas of controversy associated with CAP (antibiotic resistance, role of penicillin, risk stratification, treatment guidelines and the role of the new macrolides and fluoroquinolones).

Background

CAP is defined as an acute infection of the pulmonary parenchyma occurring in patients outside of a hospital or in patients living in a nursing home for greater than 2 weeks. (3) Common presentations of CAP may include dyspnea, cough +/- sputum production, change in sputum color, fever, chills or rigors. (3) Nonspecific constitutional symptoms such as fatigue, malaise, myalgias and loss of appetite may also be present (3). Auscultatory findings may include altered breath sounds or rales while radiologic chest findings include pulmonary infiltrates consistent with acute pneumonia. (3) It is generally accepted that signs and symptoms do not correlate with the causative organism(s).

Despite the wide availability of antimicrobials, CAP mortality remains high, ranging from 14-30% depending on patient risk factors. (3-5) Several risk factors for mortality have been identified including age (>65 years old), immunosuppression, malignancies, congestive heart failure, diabetes mellitus, alcohol consumption, neurologic disorders and laboratory abnormalities (e.g. leukopenia, neutropenia). (3-5)

Bacteriology

Factors such as alcoholism, COPD, site of care, animal exposure, travel history, structural lung disease, aspiration and concomitant viral infections. may influence the specific pathogen causing CAP. (3) The most common bacterial pathogens found in patients with CAP include *S. pneumoniae*, *H. influenzae*, *S. aureus* and atypical pathogens such as *Legionella spp.*, *C. pneumoniae* and *Mycoplasma spp.* (Table 1). (1,3) *S. pneumoniae* is the most common cause of CAP (20-60%) followed by *C. pneumoniae* (4-6 %) and *H. influenzae* (3-10%). (1) Atypical organisms have gained greater attention as pathogens in CAP over the past few years. The prevalence of atypical pathogens in CAP; however, appears variable. (6) Atypical pathogens such as *C. pneumoniae* and *M. pneumoniae* appear to be more common in the ambulatory setting. (3) In 2-5% of CAP cases, multiple pathogens are identified. (3) Other gram-positive cocci (e.g. *S. aureus*) and gram negative bacilli (e.g. *K. pneumoniae*) have also been identified as pathogens. Comparison of the prevalence of CAP pathogens among various studies have shown significant variability in prevalence which may be attributed to different definitions and diagnostic techniques employed in these studies. Despite these differences, an etiologic agent cannot be found in 40-60% of CAP cases. (3) This is further compounded by the absence of rapid diagnostic tests to identify the pathogens responsible for CAP. As a result, the majority of antibiotic therapy in CAP has been empiric.

Table 1. Common Bacterial Causes of Community-Acquired Pneumonia.*

Pathogen	Prevalence
<i>S. pneumoniae</i>	20-60%
<i>H. influenzae</i>	3-10%
<i>S. aureus</i>	3-5%
Gram-negative bacilli	3-10%
Miscellaneous**	3-5%
Atypicals	
<i>C. pneumoniae</i>	4-6%
<i>M. pneumoniae</i>	1-6%
<i>Legionella spp.</i>	2-8%

*adapted from reference 1

** including *M. catarrhalis*, group A streptococcus, *N. meningitidis*

Antibiotic Resistance

Over the past decade, the global emergence of antibiotic resistance among CAP pathogens (e.g. beta-lactamase producing *H. influenzae* or *M. catarrhalis*) has raised concerns. However, the emergence and increasing prevalence of penicillin-resistant *S. pneumoniae* (PRSP) has garnered current attention. In the United States, the prevalence of intermediate and resistant PRSP have increased from 15% in 1990 to 50% in 1997. (7) In Canada, the prevalence of PRSP in Canada increased from 2.4 % in 1988 to 13.9% in 1997-1998 combined. (8) The majority of PRSP in Canada possess intermediate susceptibility to penicillin (i.e. MIC 0.1-1 ug/mL). The reasons for the difference in the prevalence of PRSP between Canada and the USA are unknown although differences in antibiotic use between the 2 countries may contribute. It is generally accepted that the excessive use of antimicrobials increases selective antibiotic pressures resulting in the emergence of antibiotic resistant organisms. Recent data suggests the prevalence of PRSP in Canada may be declining. (9,10) In addition, recent reports have indicated that the number of antibiotic prescriptions overall in Canada has decreased by 14% during the period between 1995 to 1999. (10,11) Further study is required to monitor the trend as well as determine the etiology of the decline.

Many high-level resistant strains of PRSP (i.e. MIC > 2 ug/mL) also demonstrate co-resistance to at least one other class of antibiotics such as the macrolides. (7) In addition, fluoroquinolone resistance among *S. pneumoniae* has been associated with the increased use of ciprofloxacin in Canada. (8) The concern with PRSP has accounted for much of the recent emphasis on the newer macrolides (e.g. clarithromycin, azithromycin) and the respiratory fluoroquinolones (e.g. levofloxacin, gatifloxacin, moxifloxacin and fluoroquinolones with enhanced activity against *S. pneumoniae*). However, the increase in the use of the respiratory fluoroquinolones has been accompanied by isolated reports of fluoroquinolone resistance and treatment failures among *S. pneumoniae*. (13,14) These findings should alert clinicians that overuse of any antibiotic class could result in the emergence of antibiotic resistance.

Penicillin and *S. pneumoniae* MIC (Minimum Inhibitory Concentration)

With the increasing prevalence of PRSP, questions such as "Should penicillin be used at all?" have been raised. Current guidelines from the National Committee for Clinical Laboratory Standards (NCCLS) classify *S. pneumoniae* as penicillin susceptible (MIC <0.06 ug/mL), intermediate susceptible (MIC 0.1-1 ug/mL) and resistant (MIC >2 ug/mL). (15) These breakpoints would suggest that penicillin should only be used when *S. pneumoniae* is found to be penicillin susceptible (MIC <0.06 ug/mL). However, the NCCLS breakpoints were developed for the treatment of *S. pneumoniae* meningitis and may not be applicable for the treatment of pneumonia. (16) Additionally studies have found outcomes in patients treated with penicillin to be similar between those with penicillin susceptible or intermediate susceptible *S. pneumoniae*. (16,17) These studies suggests even patients with resistant *S. pneumoniae*, MIC between 2 ug/mL and 4 ug/mL, penicillin may remain effective. (16)

Recently, a report from the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group (DRSPTWG) proposed redefining the current NCCLS penicillin breakpoints for *S. pneumoniae*. (16) For penicillin susceptible *S. pneumoniae*, the group proposed raising the MIC from 0.06 ug/mL to $\leq$ 1.0 ug/mL. Breakpoints for intermediate susceptibility would increase to 2 ug/mL (from 0.1-1.0 ug/mL) and resistant to $\geq$ 4 ug/mL (from $\geq$ 2 ug/mL). At time of this writing, the NCCLS has not adopted these recommendations. However, recent treatment guidelines from the Infectious

Diseases Society of America (IDSA) and the Canadian Society of Infectious Diseases and Canadian Thoracic Society (CIDS/CTS) have clearly recognized that penicillin remains effective for PRSP. (3,18) Interestingly, the breakpoints for when penicillin may be used for *S. pneumoniae* are different between the US and Canada: ≤ 2 ug/mL and ≤ 4 ug/mL respectively. These may reflect differences in the prevalence of PRSP between the US and Canada. Nevertheless, for *S. pneumoniae*, penicillin appears to remain effective even for resistant *S. pneumoniae* and should be considered when *S. pneumoniae* susceptibilities are known.

Hospitalization and Risk Stratification

The majority of CAP patients are managed in the ambulatory setting with oral antibiotics. Of those requiring hospital admission, however, some investigators have found that some hospitalized patients could likely have been safely treated on an outpatient basis. Thus, in routine practice, the decision to hospitalize patients may be based on subjective rather than objective criteria. Fine and colleagues surveyed physicians who admitted patients with CAP who were at low risk of mortality. (19) The survey determined that hypoxemia, inability to maintain oral intake and lack of home care support were 3 factors that contributed to a physician's decision to hospitalize a patient with CAP. In addition, physicians overestimated the probability of mortality in patients at low risk. (19)

With respect to length of stay, McCormick and colleagues found significant interhospital variation in the length of stay among CAP patients in 4 hospitals in the US. (20) When comparing the shortest to the longest stay, there were no differences in mortality, symptoms at 30 days post admission, hospital readmission rates or the time required for patients to return to work.. These data suggests that some CAP patients were hospitalized longer than necessary. In a recent study of 20 Canadian hospitals, Feagan and colleagues found significant heterogeneity in the length of stay for CAP (median range 5-9 days). (21) These findings suggest considerable variability in the management of CAP in hospitals. Hence, there appears to be a need for objective guidelines or criteria to assist clinicians in identifying patients who require hospitalization versus those who may be managed as outpatients. Implementation of these criteria could reduce unnecessary hospital admissions and reduce the length of stay while maintaining positive outcomes.

Several studies have attempted to identify prognostic factors which predict CAP mortality. The Pneumonia Severity Index (PSI) or prediction rule has garnered the greatest attention and application. (3,5,22) The PSI is a 2 step process developed as a tool to assist physicians to identify CAP patients at low risk of mortality who may be managed as outpatients. (5) Factors associated with mortality were derived from a database of over 14,000 patients and were validated in over 40,000. The PSI screens patients based on age, co-morbidities, and physical findings to identify low risk patients (Class I) who may be safely managed as outpatients. Patients in Class II-V are assigned weighted scores based on age, co-morbidities, physical findings, radiologic and laboratory findings. (5) Based on the scores, patients are stratified into 5 risk classes. Class I patients have the lowest risk of mortality (0.1%). Class II-III patients may also be managed as outpatients since the risk of mortality was found to be $<1\%$, although some Class III patients may require a brief admission. In contrast, patients in Class IV-V generally require hospital admission due to the high risk of mortality (9-27%) (Table 2). The PSI, when utilized within a care map, for example, was found to reduce hospitalizations as well as the cost of managing patients with CAP. (23,24)

Table 2. Mortality Rate and Pneumonia Severity Index (PSI) Score

Class	PSI Score	Mortality
I	n/a	0.1%
II	<70	0.6%
III	71-90	0.9%
IV	91-130	9.3%
V	>130	27%

Adapted from reference 5.

The IDSA has recently endorsed the PSI as a prognostic tool. (3) However, IDSA and CIDS/CTS as well as the PSI authors caution that the prediction rule is a tool to predict mortality and not a method to triage patients. (3,5,18) In addition, the prediction rule does not account for other factors such as psychosocial status, medication compliance, cognitive impairment, ability to perform activities of daily living or other disease states (e.g. immunosuppression) nor does the PSI predict the need for intensive care unit admission. (3,18) Nevertheless, the PSI remains a useful tool to identify patients at low risk of mortality. Interventions such as expanded oral antimicrobial programs, rapid intravenous to oral conversion and uniform discharge and follow-up criteria appear to be as important as the PSI in reducing the number of admissions and length of stay if implemented. (18) This presents an opportunity for all stakeholders (physicians, nurses, pharmacists etc.) to participate in developing a uniform approach to the management of CAP using the described strategies.

Guidelines

Initial antimicrobial guidelines for CAP were published in the 1993 by the Canadian Infectious Diseases Society (CIDS) and the American Thoracic Society (ATS). (25,26) A comparison between the ATS and CIDS guidelines has been previously published. (27) In 1998, the IDSA published an extensive review of the management of CAP. (28) In August 2000 both the IDSA and the CIDS/CTS released the most current review of the management of CAP. (3,18) The two reviews provide excellent background information as well as current recommendations for the management and treatment of CAP. At the time of writing, both reviews as well as an editorial were available online at <http://www.journals.uchicago.edu/CID/journal/contents/v31n2.html>

Since the 1993 guidelines, there has been a substantial shift in antibiotic recommendations for CAP towards use of the macrolides (erythromycin, azithromycin and clarithromycin), beta-lactam/macrolide combinations and the respiratory fluoroquinolones in the most recent IDSA and CIDS/CTS recommendations. Although similar with respect to site of care (outpatient versus hospitalized) recommendations, the CIDS/CTS recommendations address nursing home residents as a separate category. In addition, outpatients are stratified into those with modifying factors, specifically chronic obstructive lung disease (with/without recent antibiotic or steroid exposure) versus those without modifying factors. (18) Of interest, CIDS/CTS have chosen to recommend antibiotics of first choice while IDSA listed their recommendations in no particular order. It should be noted that recommendations for antimicrobials were derived from a "consensus of experts and not entirely based on evidence from randomized clinical trials". (18)

A comparison of the two guidelines with focused recommendations for outpatients, nursing home and patients admitted to the medical ward will be discussed below. Recommendations regarding the ICU will not be discussed.

Outpatient CAP Treatment

As indicated previously, recommendations (Table 3) from IDSA and CIDS/CTS have endorsed the use of macrolides and the respiratory fluoroquinolones, shifting away from β -lactam monotherapy or co-trimoxazole recommended previously in 1993. Much of this change may be attributed to the prevalence of atypical pathogens as well as the increasing prevalence of β -lactam resistance among CAP pathogens such as *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. For the vast majority of outpatients, however, CAP is treated empirically.

Table 3. Comparison of Outpatient Antibiotic Recommendations

	First Choice	Alternate
IDSA	(in no order) doxycycline, macrolide or respiratory fluoroquinolone*. Special consideration: fluoroquinolone in older patients or those with underlying disease	amoxicillin/clavulanate OR SGC for <i>S. pneumoniae</i> or <i>H. influenzae</i>
CIDS/CTS		
no modifying factors	macrolide	doxycycline
COLD (no antibiotics / steroids)	new macrolide	doxycycline
COLD (recent antibiotics / steroids)	fluoroquinolone*	amoxicillin/clavulanate + macrolide OR SGC + macrolide
nursing home residents	fluoroquinolone OR amoxicillin/clavulanate + macrolide	SGC + macrolide

COLD = chronic obstructive lung disease

*eg. levofloxacin, gatifloxacin, moxifloxacin

SGC - second generation cephalosporin (e.g. cefuroxime, cefprozil)

Modified from reference 3,18.

Currently, the IDSA recommends doxycycline, macrolide or fluoroquinolone in no particular order for the outpatient treatment of CAP. (3) In contrast, CIDS/CTS have placed greater emphasis on the new macrolides (azithromycin, clarithromycin) and respiratory fluoroquinolones (Table 3). For patients without modifying factors or those with chronic obstructive lung disease (COLD) without recent antibiotic or steroid exposure, CIDS/CTS recommends a macrolide. (18) In nursing home patients and COLD patients with recent antibiotic exposure, CIDS/CTS recommends a respiratory fluoroquinolone as a first line agent (Table 3). The latter recommendations appear to reflect concerns with *H. influenzae*, enteric gram-negative bacteria as well as atypical pathogens. (18)

Relative to older agents (e.g. erythromycin), these agents appear to be better tolerated and have the added benefit of once or twice-daily administration. The caveat to the use of these new agents includes concerns with the potential overuse and the emergence of antibiotic resistance among these new agents. In addition, they are more expensive than the older drugs (e.g. erythromycin, co-trimoxazole) currently in use. In Canada, there has been a substantial therapeutic shift towards the new macrolides with a 245% increase in prescriptions from 1995 to 1999. (11,12) The impact

of the new macrolides or respiratory fluoroquinolones on outcome in outpatient CAP management is unknown at this time.

Inpatient General Medical Ward CAP Treatment

Currently, the IDSA recommends (in no order) an extended spectrum cephalosporin (e.g. cefotaxime) or β -lactam/ β -lactamase inhibitor in combination with a macrolide or a fluoroquinolone alone (Table 4). (3) In contrast, CIDS/CTS have recommended a fluoroquinolone alone as a first line agent for CAP in hospitalized patients with the alternative a second or third generation cephalosporin in combination with a macrolide. Of note, azithromycin monotherapy was not recommended by either group though studies involving intravenous azithromycin were recently published. (29,30) The IDSA expressed concern that the study participants were not seriously ill, the comparator was not ideal and the in vitro activity of azithromycin against *S. pneumoniae* was suboptimal. (3)

Table 4. Comparison of Antibiotic Recommendations For Patients Admitted to a Medical Ward.

	First Choice	Alternate
IDSA	extended-spectrum cephalosporin* + macrolide OR β -lactam/ β -lactamase inhibitor + macrolide OR fluoroquinolone alone (in no order)	
CIDS/CTS	fluoroquinolone**	Second generation or higher cephalosporin + macrolide

*cefotaxime/ceftriaxone

**e.g. levofloxacin, gatifloxacin, moxifloxacin

Modified from reference 3, 18.

The choice of a fluoroquinolone as a first line agent was derived from a consensus based on efficacy studies, ease of administration, cost considerations and perhaps reduced mortality compared to a β -lactam and macrolide combination. (18) The DRSPTWG, however, has recommended that respiratory fluoroquinolones be limited to patients in whom traditional agents have failed or are allergic to alternative agents or in those patients with documented PRSP with a penicillin MIC ≥ 4 ug/mL (10). Reports of fluoroquinolone resistance among *S. pneumoniae* suggest the respiratory fluoroquinolones should be reserved for selected patients. (13,14)

Treatment of Choice and Other Issues

The choice of which empiric antimicrobial agent(s) to use in the era of antimicrobial resistance has been debated. (31-34) The recommendations derived by IDSA and CIDS/CTS were based on clinical experience, in vitro activity, prevalence of pathogens, antibiotic resistance trends and randomized clinical trials. In Canada, there is a strong drive to use the macrolides and fluoroquinolones. Several questions pertaining to outcome, cost implications and concerns with resistance have continued to be posed.

The dilemma facing most institutions in Canada is whether to adopt the CIDS/CTS guidelines. In a

study of 20 Canadian hospitals, Feagan et al. found the majority of CAP patients were treated with 1 or 2 drug classes (39% and 48% respectively). (14) Our local review of 2 teaching hospitals found CAP patients were more likely to receive cefuroxime combined with a macrolide at one hospital while patients at the other hospital were more likely to receive cefuroxime monotherapy. The length of stay and duration of intravenous antibiotics were similar between the 2 hospitals. There was also wide variability in the types of oral stepdown antibiotics used. These results have generated questions regarding the CIDS/CTS guidelines and the impact of the macrolides and the fluoroquinolones on outcome.

In the past there has been a paucity of outcome data with the macrolides and fluoroquinolones. Recently retrospective and prospective cohort studies have suggested that the addition of a macrolide to a β -lactam for CAP reduced the mortality and length of stay compared to a β -lactam alone in patients hospitalized with CAP. (36-38) These reports have contributed to the recommendation to combine a β -lactam with a macrolide. With respect to the fluoroquinolones, preliminary reports have also suggested that using a fluoroquinolone alone in CAP may be associated with improved outcome or a reduction in mortality versus comparators. (18,39) However, there is insufficient data to draw conclusions regarding the fluoroquinolones at this time. At the very least, the outcomes with the new macrolides and fluoroquinolones appear similar to their comparators (older agents).

Another concern is the impact on cost of therapy with the new macrolides and fluoroquinolones. For some hospitals a therapeutic shift from older antibiotics (e.g., erythromycin, co-trimoxazole) towards the macrolides and fluoroquinolones have resulted in an increase in antibiotic expenditures. Doxycycline is a reasonable and inexpensive alternative for atypical pathogens and is probably underused. Tolerability and reduced frequency of administration with the new macrolides and fluoroquinolones, however, may at least partially offset the concerns with cost. Depending on the institutional infrastructure, intravenous azithromycin or intravenous levofloxacin may be cost-neutral relative to their intravenous comparators. A proposed advantage with these agents is their use within an expanded oral antibiotic program to convert or switch patients to oral therapy earlier while in hospital. An expected result would be a reduction in the cost of intravenous antibiotic therapy for patients hospitalized with CAP.

Lastly, institutions must also weigh concerns with the emergence of resistance among CAP pathogens as well as philosophical concerns with the expanded use of the fluoroquinolones. Ideally, data pertaining to the local epidemiology, antibiotic resistance patterns and treatment outcome of CAP should be used to guide the role of the new agents for CAP. Unfortunately, most institutions do not have local data and must rely on experts and opinion.

What to do?

The IDSA and CIDS/CTS CAP documents together provide an excellent overview of the issues and management of CAP. More importantly, these guidelines have generated considerable discussion at the local level with respect to applicability and validity. Should the CIDS/CTS guidelines be adopted? This decision is a difficult one and must take into account local epidemiology, resistance patterns, severity of illness, outcomes, drug administration and acquisition costs. Concerns with the emergence of antibiotic resistance must be also addressed. Based on our experience, the order of priorities and opinions differ from institution to institution.

In our own regional health authority, we have chosen (after considerable discussion) to recognize the role of the new macrolides and respiratory fluoroquinolones for the treatment of CAP in addition to our current practice of a β -lactam combined with a macrolide. Rather than avoid or

focus on a specific antibiotic regimen we have chosen to encourage a "balanced" approach to antibiotic prescribing. This approach also included active participation in the development of management guidelines incorporating the PSI as a prognostic tool. While the new macrolides appear to have supplanted previous erythromycin use, the fluoroquinolones for CAP have been used modestly. Concerns with antibiotic resistance were used as an opportunity to promote rational antibiotic prescribing.

Summary

It is evident that the management of CAP continues to generate discussion and analysis. Both the IDSA and CIDS/CTS guidelines represent "living" documents that are updated as information pertaining to antibiotic resistance, new agents, outcomes and prognostic tools become available (40). For many institutions, the challenge is to determine the role of these guidelines in current practice. Concerns over antibiotic resistance and the role of newer agents in CAP will continue to remain in the forefront over the next few years.

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Community-Acquired Pneumonia - What is the State of the Art?

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Abstract

Community-acquired pneumonia (CAP) is the 6th leading infectious cause of death with an incidence of 12 cases per 1000 population. In the United States, CAP accounts for 40,000-60,000 deaths and 600,000 to 1 million hospitalizations per year. The objective of this article is to review some of the issues and highlight areas of controversy in the management of CAP. *Streptococcus pneumoniae* is the most common cause of CAP, occurring in 20-60% of cases. In 40-60% of CAP cases, a bacterial cause cannot be found, necessitating empiric antibiotic therapy. The prevalence of penicillin-resistant *S. pneumoniae* (PRSP) is increasing and has now become a global concern. The emergence of PRSP has spurred an emphasis on the newer macrolides and the new fluoroquinolones. Issues such as the clinical impact of PRSP, the role of atypical pathogens in CAP and treatment guidelines have resulted in confusion as to what is the "drug of choice" for CAP. Guidelines have been developed to assist clinicians in selecting an antimicrobial agent. The evolving nature of CAP management will continue to stimulate discussion for many years to come.

J Inform Pharmacother 2000;3:336-344.

Community-acquired pneumonia (CAP) is the 6th leading infectious cause of death accounting for 40,000-60,000 deaths and 600,000 to 1 million hospitalizations per year in the United States (1). Community-acquired pneumonia is reported to occur in 2.3% of the population with an incidence of 12 cases per 1000 population (2,3). Elderly patients (often with co-morbidities) account for the majority of hospitalizations. The economic impact from CAP is significant; the annual cost of treating patients with CAP is estimated to be \$8 billion (US) (2). Significant research has been devoted to CAP over the past several years resulting in a better understanding of the

bacterial etiology, prognosis and risk factors associated with CAP. In addition, the use of management guidelines and the availability of new antimicrobial classes have provided clinicians with many treatment options. Despite these developments, questions pertaining to the management of CAP persist. The objective of this article is to briefly review CAP (definition, etiology, risk factors and prognosis) while highlighting new developments and areas of controversy associated with CAP (antibiotic resistance, role of penicillin, risk stratification, treatment guidelines and the role of the new macrolides and fluoroquinolones).

Background

CAP is defined as an acute infection of the pulmonary parenchyma occurring in patients outside of a hospital or in patients living in a nursing home for greater than 2 weeks. (3) Common presentations of CAP may include dyspnea, cough +/- sputum production, change in sputum color, fever, chills or rigors. (3) Nonspecific constitutional symptoms such as fatigue, malaise, myalgias and loss of appetite may also be present (3). Auscultatory findings may include altered breath sounds or rales while radiologic chest findings include pulmonary infiltrates consistent with acute pneumonia. (3) It is generally accepted that signs and symptoms do not correlate with the causative organism(s).

Despite the wide availability of antimicrobials, CAP mortality remains high, ranging from 14-30% depending on patient risk factors. (3-5) Several risk factors for mortality have been identified including age (>65 years old), immunosuppression, malignancies, congestive heart failure, diabetes mellitus, alcohol consumption, neurologic disorders and laboratory abnormalities (e.g. leukopenia, neutropenia). (3-5)

Bacteriology

Factors such as alcoholism, COPD, site of care, animal exposure, travel history, structural lung

disease, aspiration and concomitant viral infections. may influence the specific pathogen causing CAP. (3) The most common bacterial pathogens found in patients with CAP include *S. pneumoniae*, *H. influenzae*, *S. aureus* and atypical pathogens such as *Legionella* spp., *C. pneumoniae* and *Mycoplasma* spp. (Table 1). (1,3) *S. pneumoniae* is the most common cause of CAP (20-60%) followed by *C. pneumoniae* (4-6 %) and *H. influenzae* (3-10%). (1) Atypical organisms have gained greater attention as pathogens in CAP over the past few years. The prevalence of atypical pathogens in CAP; however, appears variable. (6) Atypical pathogens such as *C. pneumoniae* and *M. pneumoniae* appear to be more common in the ambulatory setting. (3) In 2-5% of CAP cases, multiple pathogens are identified. (3) Other gram-positive cocci (e.g. *S. aureus*) and gram negative bacilli (e.g. *K. pneumoniae*) have also been identified as pathogens. Comparison of the prevalence of CAP pathogens among various studies have shown significant variability in prevalence which may be attributed to different definitions and diagnostic techniques employed in these studies. Despite these differences, an etiologic agent cannot be found in 40-60% of CAP cases. (3) This is further compounded by the absence of rapid diagnostic tests to identify the pathogens responsible for CAP. As a result, the majority of antibiotic therapy in CAP has been empiric.

Table 1. Common Bacterial Causes of Community-Acquired Pneumonia.*

Pathogen	Prevalence
<i>S. pneumoniae</i>	20-60%
<i>H. influenzae</i>	3-10%
<i>S. aureus</i>	3-5%
Gram-negative bacilli	3-10%
Miscellaneous**	3-5%
Atypicals	
<i>C. pneumoniae</i>	4-6%
<i>M. pneumoniae</i>	1-6%
<i>Legionella</i> spp.	2-8%

*adapted from reference 1

** including *M. catarrhalis*, group A streptococcus, *N. meningitidis*

Antibiotic Resistance

Over the past decade, the global emergence of antibiotic resistance among CAP pathogens (e.g. beta-lactamase producing *H. influenzae* or *M. catarrhalis*) has raised concerns. However, the emergence and increasing prevalence of penicillin-resistant *S. pneumoniae* (PRSP) has garnered current attention. In the United States, the prevalence of intermediate and resistant PRSP have increased from 15% in 1990 to 50% in 1997. (7) In Canada, the prevalence of PRSP in Canada increased from 2.4 % in 1988 to 13.9% in 1997-1998 combined. (8) The majority of PRSP in Canada possess intermediate susceptibility to penicillin (i.e. MIC 0.1-1 ug/mL). The reasons for the difference in the prevalence of PRSP between Canada and the USA are unknown although differences in antibiotic use between the 2 countries may contribute. It is generally accepted that the excessive use of antimicrobials increases selective antibiotic pressures resulting in the emergence of antibiotic resistant organisms. Recent data suggests the prevalence of PRSP in Canada may be declining. (9,10) In addition, recent reports have indicated that the number of antibiotic prescriptions overall in Canada has decreased by 14% during the period between 1995 to 1999. (10,11) Further study is required to monitor the trend as well as determine the etiology of the decline.

Many high-level resistant strains of PRSP (i.e. MIC > 2 ug/mL) also demonstrate co-resistance to at least one other class of antibiotics such as the macrolides. (7) In addition, fluoroquinolone resistance among *S. pneumoniae* has been associated with the increased use of ciprofloxacin in Canada. (8) The concern with PRSP has accounted for much of the recent emphasis on the newer macrolides (e.g. clarithromycin, azithromycin) and the respiratory fluoroquinolones (e.g. levofloxacin, gatifloxacin, moxifloxacin and fluoroquinolones with enhanced activity against *S. pneumoniae*). However, the increase in the use of the respiratory fluoroquinolones has been accompanied by isolated reports of fluoroquinolone resistance and treatment failures among *S. pneumoniae*. (13,14) These findings should alert clinicians that overuse of any antibiotic class could result in the emergence of antibiotic resistance.

Penicillin and *S. pneumoniae* MIC (Minimum Inhibitory Concentration)

With the increasing prevalence of PRSP, questions such as "Should penicillin be used at all?" have been raised. Current guidelines from the National Committee for Clinical Laboratory Standards (NCCLS) classify *S. pneumoniae* as penicillin susceptible (MIC <0.06 ug/mL), intermediate susceptible (MIC 0.1-1 ug/mL) and resistant (MIC >2 ug/mL). (15) These breakpoints would suggest that penicillin should only be used when *S. pneumoniae* is found to be penicillin susceptible (MIC <0.06 ug/mL). However, the NCCLS breakpoints were developed for the treatment of *S. pneumoniae* meningitis and may not be applicable for the treatment of pneumonia. (16) Additionally studies have found outcomes in patients treated with penicillin to be similar between those with penicillin susceptible or intermediate susceptible *S. pneumoniae*. (16,17) These studies suggests even patients with resistant *S. pneumoniae*, MIC between 2 ug/mL and 4 ug/mL, penicillin may remain effective. (16)

Recently, a report from the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group (DRSPTWG) proposed redefining the current NCCLS penicillin breakpoints for *S. pneumoniae*. (16) For penicillin susceptible *S. pneumoniae*, the group proposed raising the MIC from 0.06 ug/mL to ≤ 1.0 ug/mL. Breakpoints for intermediate susceptibility would increase to 2 ug/mL (from 0.1-1.0 ug/mL) and resistant to ≥ 4 ug/mL (from ≥ 2 ug/mL). At time of this writing, the NCCLS has not adopted these recommendations. However, recent treatment guidelines from the Infectious Diseases Society of America (IDSA) and the Canadian Society of Infectious Diseases and Canadian Thoracic Society (CIDS/CTS) have clearly recognized that penicillin remains effective for PRSP. (3,18) Interestingly, the breakpoints for when penicillin may be used for *S. pneumoniae* are different between the US and Canada: ≤ 2 ug/mL and ≤ 4 ug/mL respectively. These may reflect differences in the prevalence of PRSP between the US and Canada. Nevertheless, for *S. pneumoniae*, penicillin appears to remain effective even for resistant *S. pneumoniae* and should be considered when *S. pneumoniae* susceptibilities are known.

Hospitalization and Risk Stratification

The majority of CAP patients are managed in the ambulatory setting with oral antibiotics. Of those requiring hospital admission, however, some investigators have found that some hospitalized patients could likely have been safely treated on an outpatient basis. Thus, in routine practice, the decision to hospitalize patients may be based on subjective rather than objective criteria. Fine and colleagues surveyed physicians who admitted patients with CAP who were at low risk of mortality. (19) The survey determined that hypoxemia, inability to maintain oral intake and lack of home care support were 3 factors that contributed to a physician's decision to hospitalize a patient with CAP. In addition, physicians overestimated the probability of mortality in patients at low risk. (19)

With respect to length of stay, McCormick and colleagues found significant interhospital variation in the length of stay among CAP patients in 4 hospitals in the US. (20) When comparing the shortest to the longest stay, there were no differences in mortality, symptoms at 30 days post admission, hospital readmission rates or the time required for patients to return to work. These data suggests that some CAP patients were hospitalized longer than necessary. In a recent study of 20 Canadian hospitals, Feagan and colleagues found significant heterogeneity in the length of stay for CAP (median range 5-9 days). (21) These findings suggest considerable variability in the management of CAP in hospitals. Hence, there appears to be a need for objective guidelines or criteria to assist clinicians in identifying patients who require hospitalization versus those who may be managed as outpatients. Implementation of these criteria could reduce unnecessary hospital admissions and reduce the length of stay while maintaining positive outcomes.

Several studies have attempted to identify prognostic factors which predict CAP mortality. The Pneumonia Severity Index (PSI) or prediction rule has garnered the greatest attention and application. (3,5,22) The PSI is a 2 step process developed as a tool to assist physicians to identify CAP patients at low risk of mortality who may be managed as outpatients. (5) Factors associated with mortality were derived from a database of over 14,000 patients and were validated in over 40,000. The PSI screens patients

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based on age, co-morbidities, and physical findings to identify low risk patients (Class I) who may be safely managed as outpatients. Patients in Class II-V are assigned weighted scores based on age, co-morbidities, physical findings, radiologic and laboratory findings. (5) Based on the scores, patients are stratified into 5 risk classes. Class I patients have the lowest risk of mortality (0.1%). Class II-III patients may also be managed as outpatients since the risk of mortality was found to be <1%, although some Class III patients may require a brief admission. In contrast, patients in Class IV-V generally require hospital admission due to the high risk of mortality (9-27%) (Table 2). The PSI, when utilized within a care map, for example, was found to reduce hospitalizations as well as the cost of managing patients with CAP. (23,24)

Table 2. Mortality Rate and Pneumonia Severity Index (PSI) Score

Class	PSI Score	Mortality
I	n/a	0.1%
II	<70	0.6%
III	71-90	0.9%
IV	91-130	9.3%
V	>130	27%

Adapted from reference 5.

The IDSA has recently endorsed the PSI as a prognostic tool. (3) However, IDSA and CIDS/CTS as well as the PSI authors caution that the prediction rule is a tool to predict mortality and not a method to triage patients. (3,5,18) In addition, the prediction rule does not account for other factors such as psychosocial status, medication compliance, cognitive impairment, ability to perform activities of daily living or other disease states (e.g. immunosuppression) nor does the PSI predict the need for intensive care unit admission. (3,18) Nevertheless, the PSI remains a useful tool to identify patients at low risk of mortality. Interventions such as expanded oral antimicrobial programs, rapid intravenous to oral conversion and uniform discharge and follow-up criteria appear to be as important as the PSI in reducing the number of admissions and length of stay if implemented. (18) This presents an opportunity for all stakeholders (physicians, nurses, pharmacists etc.) to participate in

developing a uniform approach to the management of CAP using the described strategies.

Guidelines

Initial antimicrobial guidelines for CAP were published in the 1993 by the Canadian Infectious Diseases Society (CIDS) and the American Thoracic Society (ATS). (25,26) A comparison between the ATS and CIDS guidelines has been previously published. (27) In 1998, the IDSA published an extensive review of the management of CAP. (28) In August 2000 both the IDSA and the CIDS/CTS released the most current review of the management of CAP. (3,18) The two reviews provide excellent background information as well as current recommendations for the management and treatment of CAP. At the time of writing, both reviews as well as an editorial were available online at <http://www.journals.uchicago.edu/CID/journal/contents/v31n2.html>

Since the 1993 guidelines, there has been a substantial shift in antibiotic recommendations for CAP towards use of the macrolides (erythromycin, azithromycin and clarithromycin), beta-lactam/macrolide combinations and the respiratory fluoroquinolones in the most recent IDSA and CIDS/CTS recommendations. Although similar with respect to site of care (outpatient versus hospitalized) recommendations, the CIDS/CTS recommendations address nursing home residents as a separate category. In addition, outpatients are stratified into those with modifying factors, specifically chronic obstructive lung disease (with/without recent antibiotic or steroid exposure) versus those without modifying factors. (18) Of interest, CIDS/CTS have chosen to recommend antibiotics of first choice while IDSA listed their recommendations in no particular order. It should be noted that recommendations for antimicrobials were derived from a "consensus of experts and not entirely based on evidence from randomized clinical trials". (18)

A comparison of the two guidelines with focused recommendations for outpatients, nursing home and patients admitted to the medical ward will be discussed below. Recommendations regarding the ICU will not be discussed.

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Table 3. Comparison of Outpatient Antibiotic Recommendations

	First Choice	Alternate
IDSA	(in no order) doxycycline, macrolide or respiratory fluoroquinolone*. Special consideration: fluoroquinolone in older patients or those with underlying disease	amoxicillin/clavulanate OR SGC for <i>S. pneumoniae</i> or <i>H. influenzae</i>
CIDS/CTS		
no modifying factors	macrolide	doxycycline
COLD (no antibiotics / steroids)	new macrolide	doxycycline
COLD (recent antibiotics / steroids)	fluoroquinolone*	Amoxicillin / clavulante + macrolide OR SGC + macrolide
nursing home residents	fluoroquinolone OR amoxicillin/clavulante + macrolide	SGC + macrolide

COLD = chronic obstructive lung disease

*eg. levofloxacin, gatifloxacin, moxifloxacin

SGC - second generation cephalosporin (e.g. cefuroxime, cefprozil)

Modified from reference 3,18.

Outpatient CAP Treatment

As indicated previously, recommendations (Table 3) from IDSA and CIDS/CTS have endorsed the use of macrolides and the respiratory fluoroquinolones, shifting away from β -lactam monotherapy or co-trimoxazole recommended previously in 1993. Much of this change may be attributed to the prevalence of atypical pathogens as well as the increasing prevalence of β -lactam resistance among CAP pathogens such as *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. For the vast majority of outpatients, however, CAP is treated empirically.

Currently, the IDSA recommends doxycycline, macrolide or fluoroquinolone in no particular order for the outpatient treatment of CAP. (3) In contrast, CIDS/CTS have placed greater emphasis on the new macrolides (azithromycin, clarithromycin) and respiratory fluoroquinolones (Table 3). For patients without modifying factors or those with chronic obstructive lung disease (COLD) without recent antibiotic or steroid exposure, CIDS/CTS recommends a macrolide. (18) In nursing home patients and COLD

patients with recent antibiotic exposure, CIDS/CTS recommends a respiratory fluoroquinolone as a first line agent (Table 3). The latter recommendations appear to reflect concerns with *H. influenzae*, enteric gram-negative bacteria as well as atypical pathogens. (18)

Relative to older agents (e.g. erythromycin), these agents appear to be better tolerated and have the added benefit of once or twice-daily administration. The caveat to the use of these new agents includes concerns with the potential overuse and the emergence of antibiotic resistance among these new agents. In addition, they are more expensive than the older drugs (e.g. erythromycin, co-trimoxazole) currently in use. In Canada, there has been a substantial therapeutic shift towards the new macrolides with a 245% increase in prescriptions from 1995 to 1999. (11,12) The impact of the new macrolides or respiratory fluoroquinolones on outcome in outpatient CAP management is unknown at this time.

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Inpatient General Medical Ward CAP Treatment

Currently, the IDSA recommends (in no order) an extended spectrum cephalosporin (e.g. cefotaxime) or β -lactam/ β -lactamase inhibitor in combination with a macrolide or a fluoroquinolone alone (Table 4). (3) In contrast, CIDS/CTS have recommended a fluoroquinolone alone as a first line agent for CAP in hospitalized patients with the alternative a second or third generation cephalosporin in combination with a macrolide. Of note, azithromycin monotherapy was not recommended by either group though studies involving intravenous azithromycin were recently published. (29,30) The IDSA expressed concern that the study participants were not seriously ill, the comparator was not ideal and the in vitro activity of azithromycin against *S. pneumoniae* was suboptimal. (3)

The choice of a fluoroquinolone as a first line agent was derived from a consensus based on efficacy studies, ease of administration, cost considerations and perhaps reduced mortality compared to a β -lactam and macrolide combination. (18) The DRSPTWG, however, has recommended that respiratory fluoroquinolones be limited to patients in whom traditional agents have failed or are allergic to alternative agents or in those patients with documented PRSP with a penicillin MIC ≥ 4 ug/mL (10). Reports of fluoroquinolone resistance among *S. pneumoniae* suggest the respiratory fluoroquinolones should be reserved for selected patients. (13,14)

Treatment of Choice and Other Issues

The choice of which empiric antimicrobial agent(s) to use in the era of antimicrobial resistance has been debated. (31-34) The recommendations derived by IDSA and CIDS/CTS were based on clinical experience, in vitro activity, prevalence of pathogens, antibiotic resistance trends and randomized clinical trials. In Canada, there is a strong drive to use the macrolides and fluoroquinolones. Several questions pertaining to outcome, cost implications and concerns with resistance have continued to be posed.

The dilemma facing most institutions in Canada is whether to adopt the CIDS/CTS guidelines. In a study of 20 Canadian hospitals, Feagan et al. found the majority of CAP patients were treated with 1 or 2 drug classes (39% and 48% respectively). (14) Our local review of 2 teaching hospitals found CAP patients were more likely to receive cefuroxime combined with a macrolide at one hospital while patients at the other hospital were more likely to receive cefuroxime monotherapy. The length of stay and duration of intravenous antibiotics were similar between the 2 hospitals. There was also wide variability in the types of oral stepdown antibiotics used. These results have generated questions regarding the CIDS/CTS guidelines and the impact of the macrolides and the fluoroquinolones on outcome.

In the past there has been a paucity of outcome data with the macrolides and fluoroquinolones. Recently retrospective and prospective cohort studies have suggested that the addition of a macrolide to a β -lactam for CAP reduced the mortality and length of

Table 4. Comparison of Antibiotic Recommendations For Patients Admitted to a Medical Ward.

	First Choice	Alternate
IDSA	extended-spectrum cephalosporin* + macrolide OR β -lactam/ β -lactamase inhibitor + macrolide OR fluoroquinolone alone (in no order)	
CIDS/CTS	fluoroquinolone**	Second generation or higher cephalosporin + macrolide

*cefotaxime/ceftriaxone

**e.g. levofloxacin, gatifloxacin, moxifloxacin

Modified from reference 3, 18.

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stay compared to a β -lactam alone in patients hospitalized with CAP. (36-38) These reports have contributed to the recommendation to combine a β -lactam with a macrolide. With respect to the fluoroquinolones, preliminary reports have also suggested that using a fluoroquinolone alone in CAP may be associated with improved outcome or a reduction in mortality versus comparators. (18,39) However, there is insufficient data to draw conclusions regarding the fluoroquinolones at this time. At the very least, the outcomes with the new macrolides and fluoroquinolones appear similar to their comparators (older agents).

Another concern is the impact on cost of therapy with the new macrolides and fluoroquinolones. For some hospitals a therapeutic shift from older antibiotics (e.g., erythromycin, co-trimoxazole) towards the macrolides and fluoroquinolones have resulted in an increase in antibiotic expenditures. Doxycycline is a reasonable and inexpensive alternative for atypical pathogens and is probably underused. Tolerability and reduced frequency of administration with the new macrolides and fluoroquinolones, however, may at least partially offset the concerns with cost. Depending on the institutional infrastructure, intravenous azithromycin or intravenous levofloxacin may be cost-neutral relative to their intravenous comparators. A proposed advantage with these agents is their use within an expanded oral antibiotic program to convert or switch patients to oral therapy earlier while in hospital. An expected result would be a reduction in the cost of intravenous antibiotic therapy for patients hospitalized with CAP.

Lastly, institutions must also weigh concerns with the emergence of resistance among CAP pathogens as well as philosophical concerns with the expanded use of the fluoroquinolones. Ideally, data pertaining to the local epidemiology, antibiotic resistance patterns and treatment outcome of CAP should be used to guide the role of the new agents for CAP. Unfortunately, most institutions do not have local data and must rely on experts and opinion.

What to do?

The IDSA and CIDS/CTS CAP documents together provide an excellent overview of the issues and management of CAP. More importantly, these

guidelines have generated considerable discussion at the local level with respect to applicability and validity. Should the CIDS/CTS guidelines be adopted? This decision is a difficult one and must take into account local epidemiology, resistance patterns, severity of illness, outcomes, drug administration and acquisition costs. Concerns with the emergence of antibiotic resistance must be also addressed. Based on our experience, the order of priorities and opinions differ from institution to institution.

In our own regional health authority, we have chosen (after considerable discussion) to recognize the role of the new macrolides and respiratory fluoroquinolones for the treatment of CAP in addition to our current practice of a β -lactam combined with a macrolide. Rather than avoid or focus on a specific antibiotic regimen we have chosen to encourage a "balanced" approach to antibiotic prescribing. This approach also included active participation in the development of management guidelines incorporating the PSI as a prognostic tool. While the new macrolides appear to have supplanted previous erythromycin use, the fluoroquinolones for CAP have been used modestly. Concerns with antibiotic resistance were used as an opportunity to promote rational antibiotic prescribing.

Summary

It is evident that the management of CAP continues to generate discussion and analysis. Both the IDSA and CIDS/CTS guidelines represent "living" documents that are updated as information pertaining to antibiotic resistance, new agents, outcomes and prognostic tools become available (40). For many institutions, the challenge is to determine the role of these guidelines in current practice. Concerns over antibiotic resistance and the role of newer agents in CAP will continue to remain in the forefront over the next few years.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2000;3:400.

An evaluation of the drug-device interaction between propofol and the Lifeshield[®] (LAV) needleless primary intravenous tubing system

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This unfunded study was supported by the Vancouver Hospital and Health Sciences Centre.

Context

Since the implementation of the Lifeshield[®] (LAV) needleless primary intravenous tubing system (Abbott Laboratories) at Vancouver Hospital and Health Sciences Centre (VHHSC), case reports of cracked LAV units and leaks have been anecdotally linked to the use of propofol in the operating room setting. A preliminary investigation by Abbott Laboratories showed that after 24 hours of exposure to propofol, 31 of 32 LAV units cracked upon attachment of a male adapter, and 20 of 32 units cracked at 12 hours after a 5 minute exposure to propofol. (1)

Objectives

The objective of this study was to validate the observations by the manufacturer and determine whether or not exposure to propofol with subsequent manipulation by saline syringe flushing and attachment of a male adapter would cause cracks or leaks in the LAV units.

Setting

A major Canadian tertiary care teaching hospital.

Design

Prospective observational study.

Intervention

Ten Lifeshield[®] (LAV) units (Abbott Laboratories Lot No. 62-032 NS) were randomly drawn from hospital supplies and inspected for cracks and other visible defects. Following this inspection, the units were injected with 4-5 mL of propofol (Abbott Laboratories - Lot No. 46-839Z7), a male adapter was attached, and they were allowed to sit undisturbed at room temperature for 24 hours. The LAV units were then inspected at 2, 4, 6, 14, 16, 20, and 24 hours for signs of cracks or leaks. At 24 hours, a 12 mL luer-lock syringe with a male adapter was directly attached onto each LAV unit to flush with 20 mL of normal saline solution. The units were inspected immediately after the flush, then allowed to stand undisturbed at room temperature for a further 24 hours. At the end of this period, a final visual inspection of the units was undertaken.

Main Outcome Measures

The primary outcomes of this study were visual evidence of cracks or leaks at baseline, anytime throughout the 24-hour exposure to propofol, immediately after flushing the units, and at 24 hours post-flushing.

Results

At baseline, 7 of the 10 units had visual collar markings that were deemed to be inclusions, not cracks. No cracks or leaks developed in any of the 10 units inspected during the experiment. Any visual markings on the units were unchanged after exposure to propofol.

Conclusions

We were unable to duplicate the findings of the manufacturer and found no evidence that prolonged propofol exposure to Lifeshield[®] (LAV) units causes cracks or leaks, or alters pre-existing visual markings on the units. We hypothesize that excessive lateral force, excessive torque or other factors may be the primary cause of the reported cases of device failure at this hospital. In contrast, the manufacturer has concluded that the lipid-based propofol solution is reacting with the plastic LAV components and has identified that they are initiating a corrective plan to convert to an alternate plastic material that is compatible with lipid-type solutions. In the interim, Abbott recommends that Clave-type ports be used as the material of this type of port is apparently compatible with lipids. (1)

Reference

1. Personal Communication (April 2000). Olga Powell, Director, Quality Assurance, Abbott Laboratories.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2000;3:401.

Faculty of Pharmaceutical Sciences, University of British Columbia Alan C. Hayman Summer Student Research Competition 2000

Partial Proceedings from the Faculty of Pharmaceutical Sciences Summer Student Research Program Poster Competition

Abstracts

INTEGRATION OF THE PHARMACY CURRICULUM USING WEB-BASED TECHNOLOGY

Simon P. Albon, Howard Sham, Nelson P. Kuhlen, Philip Hui, Stephanie Lee, Arthur Krumins, Kishor M. Wasan

THE APPLICATION OF LIQUID CHROMATOGRAPHY/MASS SPECTROMETRY TO THE QUALITATIVE ANALYSIS OF ILLICIT RAVE DRUGS

Rahim Kanji, Keith M. MCErlane

Development and Integration of Pharmaceutical Care Resources Using Web-Based Technology

Rosemin Kassam, Stephanie Lee

HEAT TREATMENT OF AMPHOTERICIN B MODIFIES ITS PHARMACOKINETICS AND RENAL TOXICITY IN A RABBIT MODEL, AND ALTERS ITS ACTIVITY IN THE PRESENCE OF HUMAN SERUM ALBUMIN

Evan H. Kwong, Manisha Ramaswamy¹, Emily A. Bauer, Scott C. Hartsel, Kishor M. Wasan

IMMUNOHISTOCHEMICAL ANALYSES OF ENDOTHELIN (ET) RECEPTORS IN BOSENTAN-TREATED AND UNTREATED STREPTOZOTOCIN-DIABETIC RAT HEARTS AND ARTERIES

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The Role of Serum Lipid Levels on Amphotericin B-Induced Nephrotoxicity in Pediatric Oncology Patients: Comparing 4-Day and 7-Day Therapy

Titus Wong, Eunice Wong, Lorilynn Holtorf, Traci Corr, Sheila Pritchard, Kishor M. Wasan

INTEGRATION OF THE PHARMACY CURRICULUM USING WEB-BASED TECHNOLOGY

Simon P. Albon, Howard Sham, Nelson P. Kuhlen, Philip Hui, Stephanie Lee, Arthur Krumins, Kishor M. Wasan

Objective: The objective of this project was to upgrade the Web-Based Learning Centre (WBLC) prototype created in year one of the project. Based on student feedback, a re-designed user interface is expected to further integrate the pharmacy curriculum into a unified resource to enhance teaching and learning in the pharmaceutical sciences. **Methods:** Enhancing the initial WBLC prototype involved strategic planning, creative development and production phases. Strategic planning consisted of extensive information gathering, consultations and concept mapping to clearly define the learning framework and the features critical for the new site design. The creative development process involved transcribing the entire resource on poster-sized paper into storyboards and site maps. The production phase focussed on the creation of a central menubar, homepages, course materials, graphic elements, animations and the interactivity of the centre using a number of software packages. Existing evaluation profiles in the form of two questionnaires, developed to determine the effectiveness of the prototype for student learning, were added to the site for on-line delivery. **Results:** An upgraded WBLC prototype integrating seven core pharmacy courses and Continuing Pharmacy Education (CPE) into a seamless resource was successfully created. Components of the resource include the WBLC homepage, seven WebCT courses and the CPE website. The WBLC homepage provides an overview of the resource including instructions, tutorials and recommendations on how to use the resource. WebCT courses include a homepage built on top of the WebCT framework in addition to four common elements (Course Materials, Evaluation Tools, Communications Tools and a Resource Centre). Integration of course materials are provided through strategic linking of materials within each course (Intralinks), between courses (Interlinks) and to other sites on the internet (URLinks). Integrative problems involving literature evaluation were developed to promote the use of the resource links. An intuitive menubar was developed to link all components of the centre. The interface uses a user-centric model designed around a fundamental "three clicks to anywhere" principle. The WBLC is currently being implemented and evaluated during the 2000-2001 academic year. **Conclusions:** A WWW-based educational resource was successfully created with the potential to enhance teaching and learning in the pharmaceutical sciences. The successful implementation and evaluation of this resource may provide the potential for utilizing technology-based approaches for educating students and for moving to a more learner-centered approach to pharmacy education. **Acknowledgements:** The authors would like to acknowledge generous support from the University of British Columbia's Teaching and Learning Enhancement Fund (to SPA and KMW), the Government of British Columbia's Student Summer Works Program and the Faculty of Pharmaceutical Sciences.

THE APPLICATION OF LIQUID CHROMATOGRAPHY/MASS SPECTROMETRY TO THE QUALITATIVE ANALYSIS OF ILLICIT RAVE DRUGS. Rahim Kanji, Keith M. McErlane

Purpose: The purpose of this study was to determine the identity of the various drug samples found during RCMP raids of Rave Parties. **Methods:** Each sample was triturated using a mortar and pestle and dissolved in 10 mL of mobile phase (10% acetonitrile/0.09% formic acid). These samples were further diluted and refrigerated at 4°C until required for analysis. High Performance Liquid Chromatography (HPLC) in combination with Mass Spectrometry (MS) was used to identify the unknown drugs. HPLC/MS was used in lieu of Gas Chromatography/MS or Capillary Electrophoresis/MS because it has higher sensitivity and selectivity, does not require a derivitization step and is more suitable for thermolabile compounds. The retention times of each sample were compared to fifteen known standards to help determine their identities. **Results:** Approximately 400 drug samples were analyzed. The most

prevalent drug found was 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy). The second and third most prevalent drugs found, methamphetamine and 3,4-methylenedioxyamphetamine, respectively, are also amphetamine derivatives. Conclusions: These findings suggest that amphetamines, in particular Ecstasy, are the most commonly abused drugs at Rave Parties. These results will be a valuable asset to healthcare professionals in helping them inform the public about the hazards of these illicit drugs. Acknowledgements. The authors gratefully acknowledge the RCMP for supplying the samples analyzed in this study.

Development and Integration of Pharmaceutical Care Resources Using Web-Based Technology

Rosemin Kassam, Stephanie Lee

Objectives. The hypothesis for this project is that Web-Based Learning Centre (WBLC) will facilitate learning and communication for students participating in Pharmacy 300, 402 and 403. The project consists of two phases, the developmental phase and the evaluation phase. The development phase was initiated this summer, the evaluation phase will be implemented next year. The specific study objectives for each of the phases include: (phase 1) design and integrate the three Pharmacy Practice courses 300, 402 and 403 into the upgraded WBLC; and (phase 2) evaluate the effectiveness of the WEB CT program as a tool to facilitate learning and communication. **Methods.** A plan was designed to allow for an efficient execution of the project. This planning step involved creating a fishbone diagram to identify the main components and activities to be undertaken. This was further developed into a program logic model to describe the specific activities that needed to be undertaken for each of the components, and identify objectives to help evaluate the progress of the project. Timelines and Web site maps were also proposed. The information gathering step involved consultation with the team working on WBLC and the WEB CT support group at the University of British Columbia to identify relevant WEB CT tools, and purchase of the necessary software programs. The production step consisted of designing the Pharmacy 300, 402 and 403 course web pages, drop menus, templates, course materials, resource centres and graphics. The user interface, a common menubar developed for and found on every web page in the WBLC, helped integrate these courses into the WBLC. **Results.** The research project plan was very effective in helping the team stay focused on the objectives to be achieved. The program logic model and fish-bone diagrams will be presented to provide an overview of the project plan. Three WEB CT based courses, Pharmacy 300, 402, and 403, were developed and integrated into the WBLC. Each course consisted of a homepage and four common elements: Course Materials, Evaluation Tools, Communication Tools, and the Resource Centre. Course materials and pharmaceutical care resources were integrated through linking within each course (intralinks), between courses (interlinks), and to other Internet sites (URLinks). Provisions were made to incorporate evaluation tools such as quizzes, self-assessment surveys, and clerkship evaluation forms, so students may complete and submit these tools on-line. Students may correspond and discuss course topics with fellow classmates and course instructors using the WEB CT communication tools - Private E-mail, Bulletin Board and Real-time Chat. The Resource Centre consisted of links to various pharmaceutical care resources and other internet sites to facilitate learning. Students can help further develop the Resource Centre by submitting links to additional useful internet sites to the course director using the bulletin board. **Conclusions.** The development of a web-based learning resource for Pharmacy 300, 402, and 403 was a success. These resources have the potential to enhance student learning and understanding of pharmaceutical care and its implementation in a variety of practice settings.

HEAT TREATMENT OF AMPHOTERICIN B MODIFIES ITS PHARMACOKINETICS AND RENAL TOXICITY IN A RABBIT MODEL, AND ALTERS ITS ACTIVITY IN THE PRESENCE OF HUMAN SERUM ALBUMIN

Evan H. Kwong, Manisha Ramaswamy, Emily A. Bauer, Scott C. Hartsel, Kishor M. Wasan

Purpose: The purpose of this project was to study the heat-treated form of Amphotericin B. Its pharmacokinetics, distribution in serum lipoproteins and tissues, and renal toxicity were determined for a single dose in rabbits. In addition, its activity against model mammalian and model fungal membranes in the presence of human serum albumin (HSA) was examined. **Methods:** Fungizone (FZ) solutions were heated at 70°C for 20 minutes to produce Heat-treated Fungizone (HFZ). **Rabbit Study.** A single intravenous dose of FZ or HFZ at 1mg/kg was administered to female New Zealand white rabbits. Blood samples were obtained before drug administration and serially thereafter. After the 48-hour blood sample, each rabbit was humanely sacrificed. Serum creatinine levels were measured before and 10 hours after drug administration. Amphotericin B levels in the serum were analyzed using High Performance Liquid Chromatography. **Activity Study.** Model mammalian and model fungal membranes were made by extrusion. The membrane ion channel forming activities of HFZ and FZ against these membranes were compared using an Applied Photophysics stopped flow spectrometer with fluorimeter detector. **Results:** HFZ shows decreased kidney toxicity compared with FZ. HFZ follows a two-compartment model, with a similar apparent volume of distribution to FZ. However, HFZ clears faster from the system than FZ. In the presence of HSA, the activity of HFZ against model mammalian membranes is lower than that of FZ, yet it is still effective against model fungal membranes. **Conclusions:** Heat-treated Fungizone is an improved low-cost Amphotericin B drug delivery system that has a potentially higher therapeutic index than regular Fungizone. **Acknowledgements:** Medical Research Council of Canada (grant #MT-14484 to KMW), National Science Foundation (MCB-9603582 to SCH), Rx&D Health Research Foundation / Canadian Institutes of Health Research (to EHK), and Ronald E. McNair Scholars Program (to EAB).

IMMUNOHISTOCHEMICAL ANALYSES OF ENDOTHELIN (ET) RECEPTORS IN BOSENTAN-TREATED AND UNTREATED STREPTOZOTOCIN-DIABETIC RAT HEARTS AND ARTERIES Inna Sekirov, Emi Arikawa, John H. McNeill

Purpose. Evidence has shown that endothelin-1 (ET-1), a 21 amino-acid vasoconstrictor-mitogen, may be involved in mediating cardiovascular complications in diabetes. Previous studies from our laboratory have demonstrated that the ET-1 level is increased in diabetic rat hearts and arteries, and that treatment with bosentan, an ETA and ETB receptor antagonist, ameliorates the impaired cardiac function and normalizes the enhanced vascular contractile responses in diabetic rats. The purpose of this study was to examine the expression of ETA and ETB receptors in diabetic rat tissues, and to determine whether the beneficial action of bosentan in alleviating diabetes-induced cardiovascular abnormalities is related to the level of ETA and ETB receptors. **Methods.** Wistar rats were randomly divided into four groups: control (C), control bosentan-treated (CB), diabetic (D) and diabetic bosentan-treated (DB). Diabetes was induced with streptozotocin (STZ; 60mg/kg iv) in D and DB rats. One week after STZ-injection, CB and DB rats received bosentan treatment (100mg/kg/day po). After 10 weeks of bosentan treatment, ventricles, aortae, superior mesenteric and renal arteries were isolated from the four rat groups. Paraffin-embedded sections of those tissues were prepared and analyzed by immunohistochemistry for the levels of ETA and ETB receptors. Images of the stained tissues were obtained, and the ETA and ETB receptor immunoreactivity in each tissue was subsequently measured using Northern Eclipse computer software. **Results.** In the presence of diabetes, ETA-like immunoreactivity (ir) and ETB-like ir in ventricular tissues as well as ETA-like ir in renal arteries were significantly reduced when compared to the control tissues. The level of both ETA and ETB receptors was unchanged in D aortae and superior mesenteric arteries, as was the level of ETB in D renal arteries. Bosentan did not affect the ETA level in the diabetic tissues. The level of ETB was, however, restored

to control levels in both right and left diabetic ventricles by bosentan treatment. Moreover, an increase in ETB-like ir was observed in DB aorta, when compared to untreated D rat tissues, suggesting a bosentan-induced up-regulation of ETB in diabetic rats. In CB rats, a reduced ETA-like ir was found in the ventricles, and a decreased level of ETB in the aortae and renal arteries. Conclusions. Results from this study indicate that the level of ET receptors was either decreased or unchanged in diabetic rat ventricles and arteries. The effects of bosentan on the levels of ET receptors seem to be receptor and tissue-specific. The results suggest that the corrective action of bosentan in normalization of diabetes-induced cardiac and vascular functional abnormalities may not be mediated simply by modulating the level of ETA and ETB receptors. Further studies will be required to uncover the exact mechanism(s) underlying the beneficial effects of bosentan. Acknowledgements. This study was supported by a grant from CDA and MRC. Inna Sekirov is a recipient of a Heart and Stroke Foundation of BC and Yukon Summer Studentship.

COMPARISON OF THE EFFECTS OF WITHDRAWAL FOLLOWING CHRONIC ADMINISTRATION OF INSULIN OF BMOV IN STZ DIABETIC RATS

Osric Sin, Violet G. Yuen, John H. McNeill

Purpose: Bis(maltolato)oxovanadium(IV) (BMOV) is an effective glucose lowering agent, as is insulin, the conventional treatment of choice in diabetes mellitus. However, while insulin treatment requires injections one or more times a day BMOV is an orally effective drug. A single acute oral administration of BMOV in diabetic rats has been found to maintain a lower blood glucose level over an extended period of time. It was of interest therefore to investigate the effects of withdrawal following chronic BMOV administration and compare it with the effects of withdrawal following chronic insulin administration. Results: It was found that both treatments significantly decreased plasma glucose levels as compared to the non-treated diabetic rats ($D=31\pm1\text{mM}$, $DI=16\pm3\text{mM}$ and $DV=10\pm1\text{mM}$). At 24 hours after treatment withdrawal, plasma glucose levels in the BMOV-treated group were found to be significantly lower than the insulin-treated animals and the diabetic animals ($D=30\pm2\text{mM}$, $DI=24\pm4\text{mM}$ and $DV=14\pm3\text{mM}$). By 48 hours there was no difference in plasma glucose levels among the groups. Conclusion: This study demonstrates that chronic administration of both insulin and BMOV treatment significantly lowers blood glucose in diabetic rats. At 24 hours after treatment withdrawal there is a lower rate of reversion to a diabetic state in BMOV treated animals as opposed to insulin treated animals, but within 5 days the majority of animals in both groups had reverted back to the diabetic state.

A COMPARISON OF TOPICAL ANAESTHETICS FOR PERCUTANEOUS for percutaneous analgesia in pediatric patients

S. Verma, L. Boshell, A. Smith, D. Blackstock, B. Miller, B. Carleton

Purpose: This study consisted of two phases. The objective of Phase 1 was to conduct a pilot assessment of the safety and effectiveness of a newly developed local anaesthetic compared to a commercially prepared product (Ametop^R, Smith & Nephew) in healthy adult volunteers. The objective of Phase 2 was to determine the safety and efficacy of the new anaesthetic preparation relative to two commercially available preparations (EMLA^R, lidocaine and prilocaine aa 2.5%, ASTRA Pharma, and Ametop^R) prior to venous cannulation in pediatric patients undergoing daycare surgery. Methods: Phase 1 was a double-blind cross-over trial in 40 healthy adult volunteers. 2g of tetracaine 4% w/w (Ametop^R) was applied to the antecubital fossa of one arm, and 2g of the newly formulated tetracaine preparation was applied to the other arm in the same location. Efficacy of analgesia was measured using a calibrated pin-prick

device at various intervals (15, 20, 25, 30, and 45 minutes after application of the cream). Study participants rated the degree of analgesia using a three-point scale. Two formulations of the study cream were tested, each with a differently formulated cream base. Phase 2 was a double-blind randomized trial in pediatric patients undergoing daycare surgery. Patients received either 2g of EMLA^R, 1g of Ametop^R, or 2g of the study cream, 60 minutes, 45 minutes, or 35 minutes respectively prior to venous cannulation on the dorsal aspect of their left hand. The patient's pain was assessed using the 7 point Bieri Faces Pain Scale (1 being no pain and 7 being the greatest pain). Side effects were assessed at the time of cannulation 1-5 hours after application of the cream. Results: With the first study cream formulation (n=22), 4 volunteers felt no anaesthesia, 7 felt partial and 11 felt full anaesthesia at 30-35 minutes after application of the cream. With Ametop^R, 1 volunteer felt no anaesthesia, 5 felt partial, and 16 felt full anaesthesia at 30-35 minutes. At 45 minutes, 1 volunteer felt no anaesthesia, 1 felt partial, and 20 felt full anaesthesia with both the study cream and Ametop^R. With the second study cream formulation (n=18), 1 volunteer felt no anaesthesia, 9 felt partial, and 8 felt full anaesthesia at 30 minutes after cream application. With Ametop^R on for 30 minutes, 3 volunteers felt no anaesthesia, 8 felt partial, and 7 felt full anaesthesia. At 45 minutes with the study cream, 2 felt no anaesthesia, 3 felt partial, and 13 felt full anaesthesia. With Ametop^R on for 45 minutes, 3 volunteers felt no anaesthesia, 1 felt partial, and 14 felt full anaesthesia. Data is still being collected for Phase 2. Thus far, the 15 patients that received the study cream reported an average Bieri Pain Measurement of 4. The 16 patients that received EMLA^R also reported an average pain measurement of 4, and the 14 patients that received Ametop^R reported an average pain measurement of 3. The standard deviation values for all three study groups overlapped. Conclusion: From Phase 1, it can be concluded that the second study cream appeared as effective as Ametop^R at the 30-35 minute mark and, therefore, the 35 minute mark for the study cream could be tested on children in Phase 2. Preliminary results from Phase 2 suggest that the new formulation may be as effective as commercially available products. Further testing in pediatric patients is required to determine equivalence. Acknowledgements: Apotex/PACE & Mount St. Joseph's Children's Center Staff

The Role of Serum Lipid Levels on Amphotericin B-Induced Nephrotoxicity in Pediatric Oncology Patients: Comparing 4-Day and 7-Day Therapy
Titus Wong, Eunice Wong, Lorilynne Holtorf, Traci Corr, Sheila Pritchard, Kishor M. Wasan

Purpose: A previous study found several correlations between the pre-Amphotericin-B (AmpB) therapy lipid profile of subjects and AmpB-induced nephrotoxicity (as measured by Day 4 serum creatinine levels). The objective of this current study is to determine whether the relationships found during 4-day AmpB therapy also exist during 7-day therapy. Rationale: Adult populations receiving AmpB usually exhibit AmpB-induced nephrotoxicity between days 7-10 of therapy. Since the previous study measured Day 4 serum creatinine levels, there was some concern that the values measured were not representative of normal AmpB therapy. Methods: The target population was all patients (age<17 years) at the British Columbia Children's Hospital receiving AmpB due to a suspected or confirmed fungal infection. Samples of patients' plasma were separated into the a (HDL) fraction by lipoprotein precipitation. Total plasma and fraction cholesterol [C] and Triglycerides [TG] levels were determined by enzymatic colorimetric assays. Plasma creatinine levels were obtained from the patients' charts. Results: For 7 day therapy, a positive correlation between Cumulative Dose and % increase in serum creatinine was found in all subjects (n=10, r=0.919, p<0.001) was found. A negative correlation between % increase in serum creatinine and Total TG for all subjects (n=10, r=-0.804, p<0.01) was found. Other correlations previously found in 4-day therapy were not found in 7 day therapy. Conclusion: Contrary to the hypothesis, LDL-C was not a predictor of AmpB-induced nephrotoxicity. However, it was found that

increases in Total-TG correlated with lower AmpB-induced nephrotoxicity. Acknowledgements: Funding for this project was provided by the Medical Research Council of Canada (grant # MT-14484) and by the British Columbia Research Institute for Women's and Children's Health.

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Research Abstracts

The Journal of Informed Pharmacotherapy 2000;3:402.

Development of a palmtop relational database for providing pharmaceutical care in a tertiary care intensive care unit

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Canadian Society of Hospital Pharmacists (British Columbia Branch) Residency Research Presentation Night, Vancouver, British Columbia, Canada. May 10, 2000. This study was funded by a grant from the the Simon Fraser Health Region Job Enrichment Program and an unrestricted grant made available through Green Shield Benefits Association.

Context

Pharmacy is an information intensive profession where increasing responsibilities and demands on time necessitate the effective use of technology. Personal digital assistants (PDAs) are handheld devices that provide computing and communications abilities. The purpose of this project was to improve data and information processing in clinical practice by integrating PDAs into the patient care process.

Objectives

To design an electronic template on a PDA for providing pharmaceutical care in the Intensive Care Unit (ICU). To assess the feasibility of a PDA as a pharmaceutical care monitoring tool. To automatically generate drug cost savings reports using standard office spreadsheet software.

Setting

A 12-bed Canadian tertiary care intensive care unit.

Design

The current means of providing pharmaceutical care was characterized, software and hardware for replicating paper forms were selected, pertinent data fields were chosen, and a database was developed. ICU patient data and pharmacists' recommendations were manually recorded on the PDA. The feasibility of integrating PDAs into an ICU practice was assessed by subjective user evaluation.

Main Outcome Measures

The outcome measures were the production of an electronic patient monitoring template, a subjective user feasibility assessment and generation of pharmacist initiated drug cost savings reports.

Results

Providing pharmaceutical care in the ICU currently follows the pharmacist's work-up of drug therapy with paper-based documentation. Hardware and software selected include a Palm Ille (Palm Inc.), HanDBase v2.01g, HanDJet 2.4, Microsoft Access 97, and Microsoft Excel 97. The patient monitoring template design consisted of three sets of linked databases. Using data collected on the PDA, cost savings reports were generated. The PDA relational database was determined to be a useful pharmaceutical care monitoring tool in the ICU.

Conclusions

We developed a feasible electronic patient monitoring template for providing pharmaceutical care in the ICU and generated cost savings reports from collected data.

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Pharmacotherapy on the Web

The Journal of Informed Pharmacotherapy 2000;3:500.

The Institute for Safe Medication Practices, The Oxford Pain Internet Site, Pneumotox Online, HONmedia Medical Images Library, EKG World Encyclopedia, NoFreeLunch.org

JIP Site Evaluation Process

Submit your own review of this or any other site

The Institute for Safe Medication Practices, The Oxford Pain Internet Site, Pneumotox Online, HONmedia - Medical Images Library, EKG World Encyclopedia, NoFreeLunch.org

Name of site:	The Institute for Safe Medication Practices NEW!
Type of site:	Information site promoting safe medication practices
Authoring organization:	The Institute for Safe Medication Practices, Huntingdon Valley, Pennsylvania, USA. Institute for Safe Medication Practices Canada, Richmond Hill, Ontario.
Sponsors:	Non-profit organization made up of Pharmacists, Nurses, and Physicians.
Of particular interest to:	Directors of Pharmacy, Nurses , Physicians , Risk Managers, Product Managers.
Completeness Score (/5)	3
Credibility Score (/5)	5
Usability Score (/5)	4
Why is it useful? (what will it help me DO?):	May be a relatively "low yield" site for the day to day needs of a practicing clinician. The site is of use to system administrators wishing to implement system safeguards for minimizing medication dispensing errors. Provides a method for voluntary self reporting of medication errors and rapid dissemination of medication safety-related information involving drug distribution, naming, packaging, labeling, computer program design and drug delivery system design.

Commentary: This site is devoted to providing education about adverse drug events and their prevention. ISMP provides several publications that may help hospitals self-evaluate their medication systems and heighten awareness of the distinguishing characteristics of a safe system. The site provides a monthly collection of medication safety alerts targeted to health professionals and consumers. A variety of safety related subscription materials and consulting services are offered for sale. Independent review of medication errors that have been voluntarily submitted by practitioners to a national Medication Errors Reporting Program operated by the United States Pharmacopeia (USP) in the USA are available.

www.ismp-canada.org is the Canadian sister site to the Institute for Safe Medication Practices in the U.S. The intent of the site is the same for both countries. The publications and services available are not yet as extensive as those available from the American counterpart.

URL of site: <http://www.ismp.org> (USA)
<http://www.ismp-canada.org> (CANADA)

Reviewed by: [Robert M. Balen](#), Pharm.D.

Name of site: **The Oxford Pain Internet Site**

Type of site: Therapy for pain specialty site.

Authoring organization: Bandolier, a British NHS-funded Print & Electronic Journal

Sponsors: BUPA Foundation and Merck Sharp and Dohme (Britain)

Of particular interest to: Clinicians who treat any type of pain and patients who experience pain.

Completeness Score (/5) 4.5

Credibility Score (/5) 4.5

Usability Score (/5) 4.5

Why is it useful? (what will it help me DO?): This site forms an excellent launching point for inquiries and systematic reviews (qualitative and quantitative) concerning treatments for pain of all types. Topics range from chronic cancer pain to migraine to non-pharmacologic treatments.

Commentary: This is a thoroughly evidence-based site which attempts to catalogue a significant proportion of the pain management literature through qualitative and quantitative systematic reviews. The systematic reviews are well summarized and appear to be rigorously conducted. They are not as methodologically transparent as Cochrane Reviews, however, but are more wide-ranging. The site is updated regularly and focuses on contemporary drug therapy issues. Check out the "League Table of Analgesics" which summarizes the NNT to produce 50% pain reduction for a multitude of analgesics.

URL of site: <http://www.jr2.ox.ac.uk/bandolier/booth/painpag/index.html>

Reviewed by: Peter Loewen, Pharm.D.

Name of site: **Pneumotox Online**

Type of site: Database of pulmonary toxicities of drugs.

Authoring organization: The French group, GEPP (Groupe d'Etudes de la Pathologie Pulmonaire latrogène)

Sponsors: SPLF (Société de Pneumologie de Langue Française) and the AFCP (Association Française des Centres de Pharmacovigilance)

Of particular interest to: Any clinician who diagnoses or treats drug-induced pulmonary diseases.

Completeness Score 5
(/5)

Credibility Score (/5) 5

Usability Score (/5) 5

Why is it useful? (what will it help me DO?): Have you ever encountered a patient with pulmonary infiltrates and wondered whether it could have been caused by a drug? This site is the fastest and most up-to-date way to find out.

Commentary: This invaluable resource has a single purpose: to catalogue reports of pulmonary toxicities of drugs. Users can search by drug to see whether it has been reported to cause pulmonary toxicity (and the radiographic findings reported) or search by radiographic pattern to see lists of drugs which may produce them. The site is extensively referenced and completely up to date. There is even a feature which allows clinicians to submit case-reports for inclusion in the database.

URL of site: <http://www.pneumotox.com>

Reviewed by: Peter Loewen, Pharm.D.

Name of site: **HONmedia Medical Images Library**

Type of site: Repository of Medical Images

Authoring organization: Health On the Net Foundation

Sponsors:

Of particular interest to:	Clinicians who give presentations and use medical illustrations to enhance them.
Completeness Score (/5)	4
Credibility Score (/5)	4
Usability Score (/5)	4
Why is it useful? (what will it help me DO?):	Allows one-stop shopping for images when generating teaching materials or presentations, or simply trying to better understand an issue (a picture tells a thousand words).
Commentary:	HONmedia is an unique repository of over 1,650 medical images and videos, pertaining to 1,200 topics and themes. Images range from photos of patients to illustrations to radiographic images to chemical structures of drugs. The images are generally of high quality and are mostly suitable for cutting and pasting into presentations and documents. Credit info is provided so proper acknowledgement is possible. Presumably images cannot be used for financial gain without permission from their authors.
URL of site:	http://www.hon.ch/HONmedia/
Reviewed by:	Peter Loewen, Pharm.D.

Name of site:	EKG World Encyclopedia
Type of site:	ECG interpretation database and teaching
Authoring organization:	The Online Journal of Cardiology
Sponsors:	McGill University, private donors, two pacemaker manufacturers.
Of particular interest to:	Clinicians who work with cardiac patients who wish to hone their ECG interpretation skills.
Completeness Score (/5)	4
Credibility Score (/5)	4
Usability Score (/5)	4
Why is it useful? (what will it help me DO?):	Provides an opportunity to practice ECG interpretation using actual case examples.
Commentary:	ECG interpretation skills are best honed through practice in actual patient situations. This site provides a large array of different scenarios ranging from the common to the very rare. Users can challenge themselves by making the diagnosis, or review ECG's organized by category (eg. Myocardial infarction, ventricular hypertrophy, implanted devices). Regardless of your profession, this is a useful site for improving your ECG interpretation skills.
URL of site:	http://www.mmip.mcgill.ca/heart/egcyhome.html
Reviewed by:	Peter Loewen, Pharm.D.

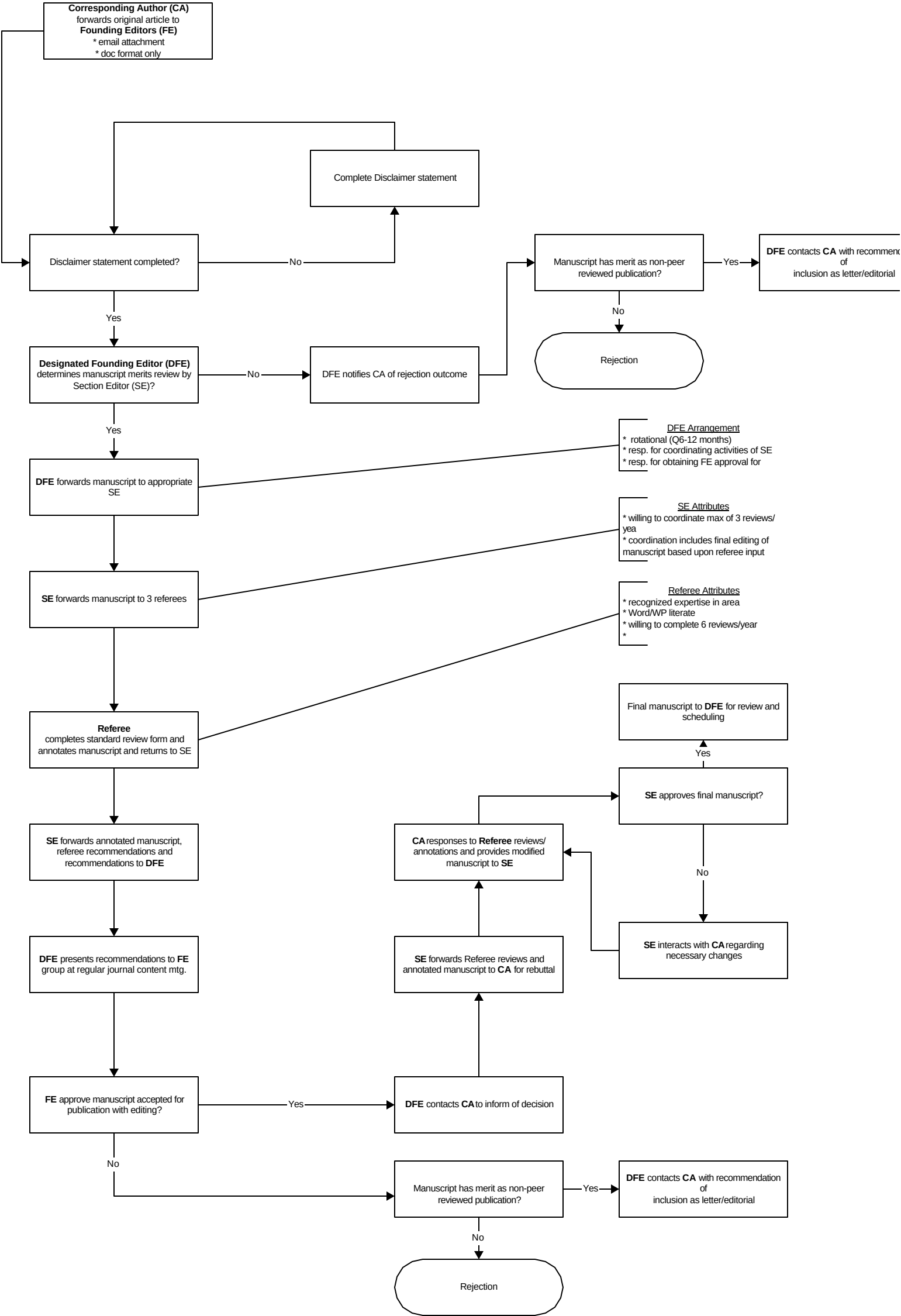
Name of site:	No Free Lunch
Type of site:	Information site opposing marketing practices of the pharmaceutical industry.
Authoring organization:	Bob Goodman, MD, a family practitioner in New York City
Sponsors:	A non-profit society made up of physicians, pharmacists, nurses, dentists concerned about the effects of pharmaceutical industry marketing on patient care.
Of particular interest to:	All health care providers.
Completeness Score (/5)	5
Credibility Score (/5)	4
Usability Score (/5)	3
Why is it useful? (what will it help me DO?):	Creates awareness about the negative effects of drug company marketing on patient care.
Commentary:	This site, whose bias against the marketing practices of the pharmaceutical industry is obvious, is extremely interesting, especially for those who are unaware of the documented effects of those practices on patient care. The site catalogues an impressive collection of literature from medical journals and the lay press about this issue. Regardless of your views on this hot topic, the site is very credible in that every statement (see the Pharmaceutical Facts and Fallacies section) is referenced and verifiable. Check out the "Pen Amnesty Program" wherein you send them your free drug company pens and they will replace them with a "nofreelunch" pen.
URL of site:	http://www.nofreelunch.org/
Reviewed by:	<u>Peter Loewen</u> , Pharm.D.

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First Author's Name and Manuscript Title:

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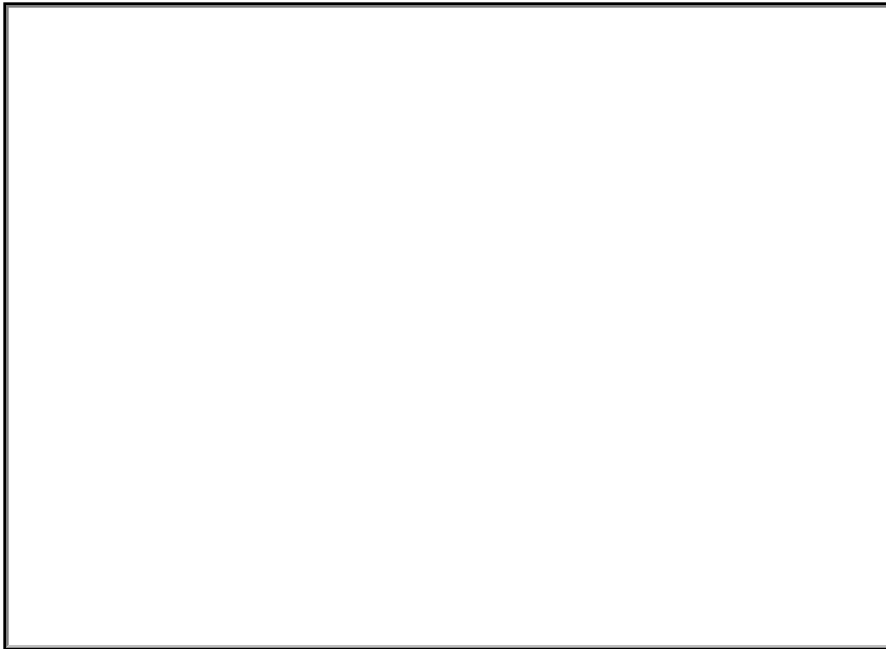
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