

# Effect of inflammation on the pharmacokinetics and pharmacodynamics of the calcium channel blocker, Nifedipine

Husam M. Younes, PhD



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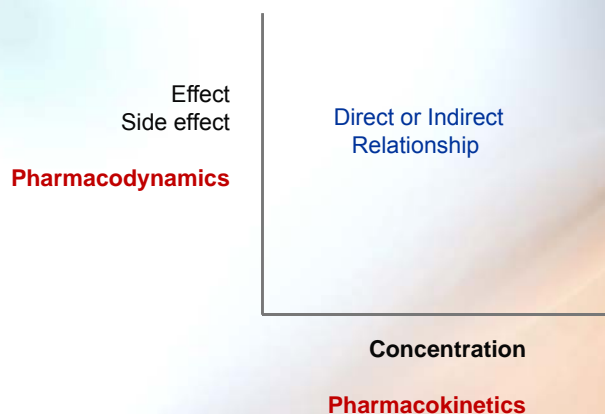
## Acknowledgments

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- Dr. Reza Tabrizchi.
  
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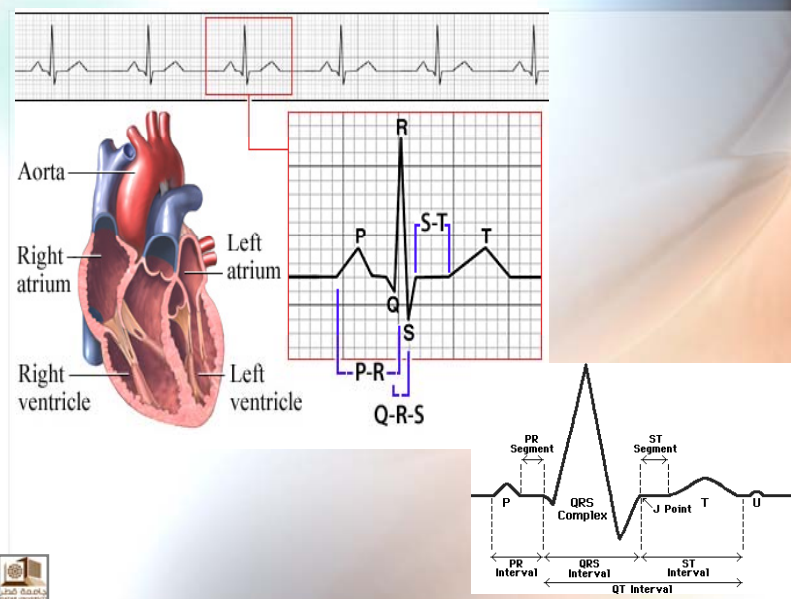
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## Pharmacology &/or Cokinetics!



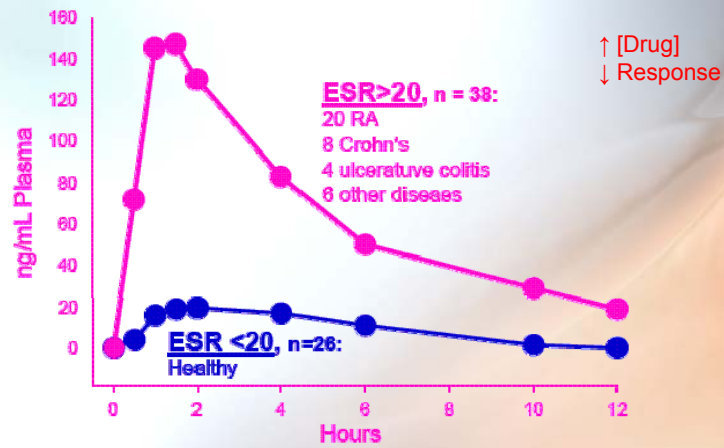
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## ECG Components: Dynamics



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## Propranolol (40 mg)



Schneither RE et al, *Int J Clin Pharmacol Ther Toxicol* 19:158-162,1981



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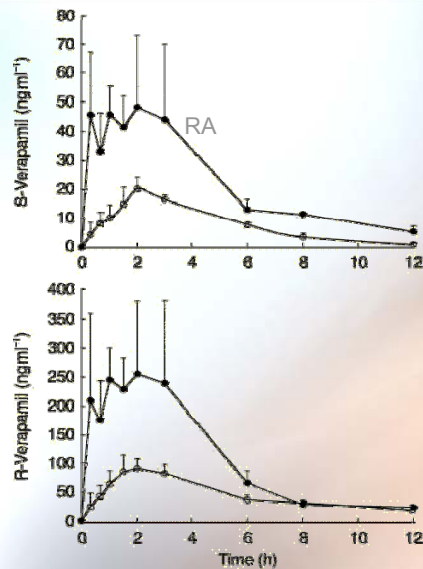
## Therapeutic Consequence?

- Increased concentration !
- Inflammation is implicated in many diseases and conditions.
- How to correlate PD with PK here?



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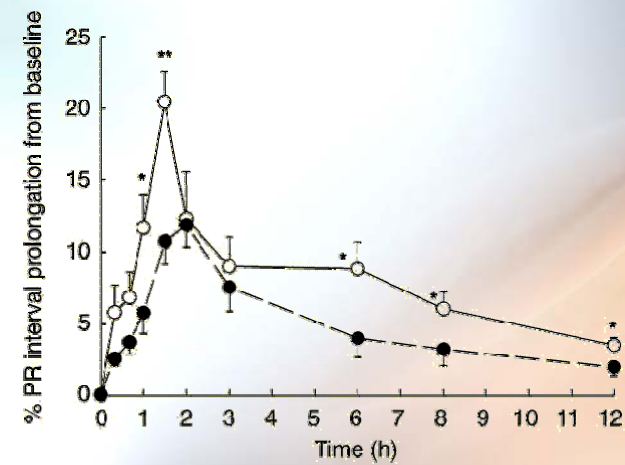
## Verapamil



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Mayo PR et al, *J Clin Pharmacol*, 50: 605-613, 2000

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## Calcium Channel Blockers

- Calcium Channel Blockers (CCBs) are important group of drugs extensively used for antihypertensive therapy over two decades
- They possess wide range of cardiac and hemodynamic effects.
- The cardiac effects involve mainly
  - prolongation of sinoatrial (SA) and atrioventricular (AV) ECG intervals.
- The hemodynamic effects involve
  - vasodilatation
  - reduction of venous return to the heart resulting in decrease of systemic blood pressure and
  - decrease in preload /afterload of the heart



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## CCBs

- CCBs are distinguished by their mechanisms by which they affect the CV.
- Divided into two major groups based on their mechanism on the CV:
  - “*Verapamil Type*” (phenylalkylamines)
  - “*Nifedipine Type*” (dihydropyridines)
- A third group, benzothiazepines (e.g. diltiazem) have equally potent cardiac and arterial effects
- “*Verapamil type*”: possess cardiodepressive effects (-ve inotropic, chronotropic, and dromotropic)
- “*Nifedipine Type*”: possess prominent hemodynamic or vascular effects (vasodilatation, changes in preload/afterload)



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## CCBs: Nifedipine (NF)



- Nifedipine is an L-type slow calcium-channel blocker used mostly for coronary artery disease, Raynaud's phenomenon, and hypertension.
- NF is highly bound to albumin (92-98%), AAG, LDL, and HDL



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- NF almost completely absorbed from the jejunum after p.o. dose.
- Extensive first-pass metabolism by gut and liver enzymes (43-77%)
- Volume of distribution,  $V_d/F$  is about 1.32 L/kg, elimination  $t_{1/2}$  ranges from 4-16 hr depending on the dosage form administered (orally)



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## Inflammation Mediators

- Pro-inflammatory cytokines such as the Interleukins 1 & 6 and Tumor Necrosis Factor (TNF- $\alpha$ ) are involved in a cascade effect leading to the redness, pain, swelling, and fever associated with inflammation.
- Interferon (IFN- $\gamma$ ) is one of the cytokines that is found at increased levels in the blood stream during the inflammation process



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- IFN- $\gamma$  is partly responsible for the chemotaxis of macrophages to the site of inflammation.
- There is also increased levels of vasodilators such as nitric oxide (NO).



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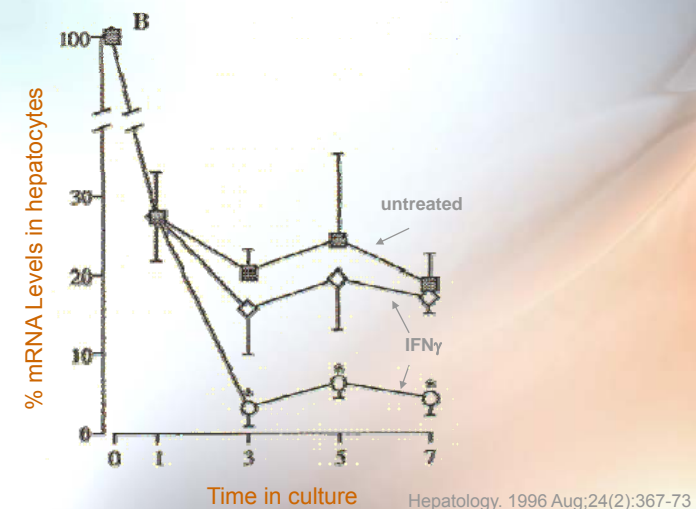
## Some Background

- There are a number of studies which support the fact that cytokines and IFN- $\gamma$  in particular down regulate the CYP450 enzymes.
- It would therefore follow that there may be a disease-drug interaction between NF and inflammatory conditions.



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## IFN- $\gamma$ and CYP3A



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## Hypertension & Inflammation

- 3.3 million Canadians have hypertension.
- 3.9 million Canadians and 15% of Newfoundlanders have arthritis.
- 300 000 Canadians specifically have rheumatoid arthritis.
- 15% of North Americans have Hypertension and some sort of inflammatory condition.



Source: Statistics Canada & Canadian Arthritis Association

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## Hypothesis

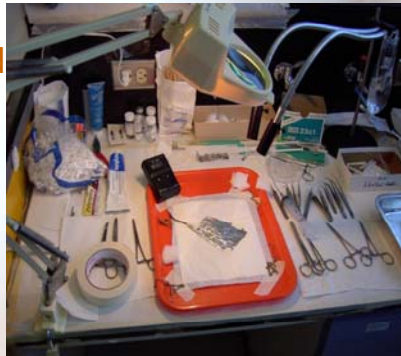
- Induction of acute inflammation triggered by subcutaneous injections of murine IFN- $\gamma$  to rats will cause changes in the PK and PD profiles of the calcium channel antagonist, Nifedipine



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## Methodology

- Using Sprague-Dawley rats, we compared the PK and PD of inflamed and control groups that were orally administered the calcium channel blocker, NF



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## Methodology

- Animals were acclimatized to the lab environment for at least 2 days prior to involvement in experiment.
- Rats were anesthetized prior to surgery and an incision is made above the clavicle on the left side of the rat.
- The left jugular vein and carotid arteries are catheterized and then exteriorized at the dorsal nape of the neck



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## Blood Sampling & Dynamics

- The jugular vein catheter was used to draw blood samples during the experiments
- 0.2 mL was taken at time intervals of 0, 10, 15, 20, 30, 60, 120, 240, 360, and 480 minutes.
- The carotid artery catheter was used to measure mean arterial blood pressure (MAP).



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## HPLC Analysis

- The Plasma was separated from the hematocrit and NF was then extracted from the samples.
- High Performance Liquid Chromatography was used to analyze the NF concentrations in the samples.



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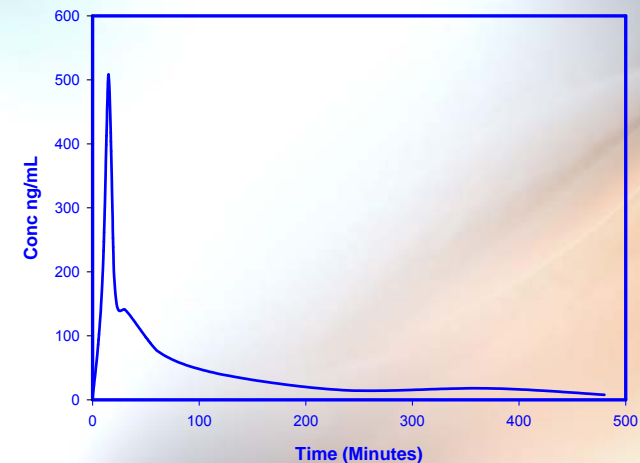
## Methodology: Summary

- Male sprague-Dawley rats (300-350 g)
- Jugular vein catheterization.
- Carotid artery catheterization (for BP measurements).
- ECG electrodes (PR interval and HR)
- Oral administration of NF by oral gavages.
- Induction of inflammation by sc injection of murine IFN-g (80,000 IU) 12 hours prior to NF dosing.
- Blood sampling withdrawn 0-8 h and plasma analyzed for NF using HPLC



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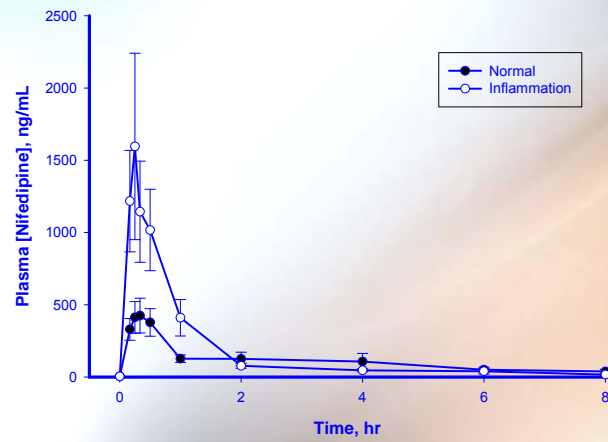
Plasma concentration profile of NF orally administered to one rat



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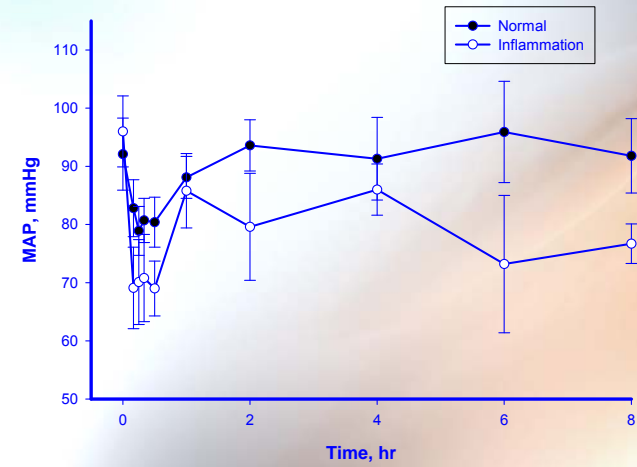
# PK Results

Effect of Acute Inflammation on Nifedipine Plasma Concentration Variations after oral administration (3 mg/kg) n=7



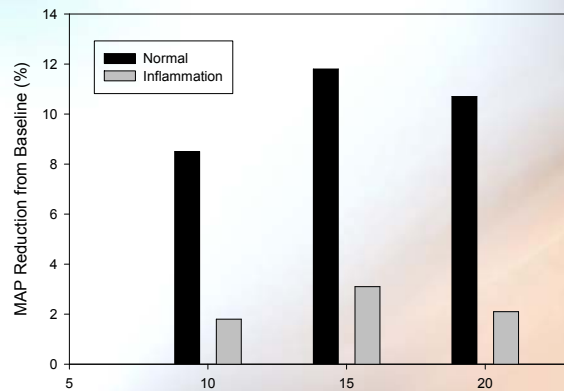
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Effect of Acute Inflammation on Nifedipine Mean Arterial Pressure Variations after oral administration (3 mg/kg) n=7



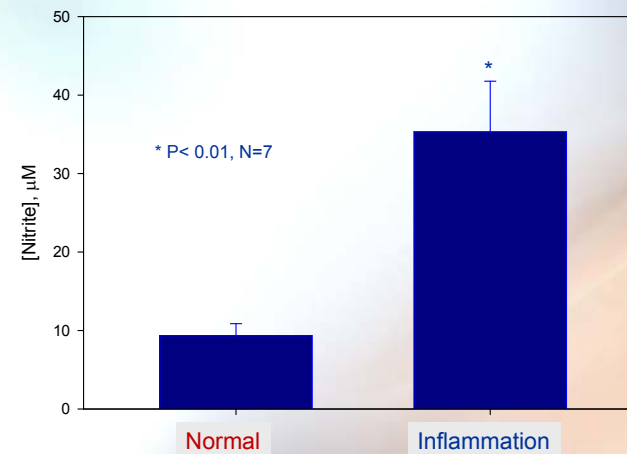
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Effect of inflammation on MAP reduction after 3 mg/kg p.o. NF during maximum drug plasma concentration (n=7)



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Effect of Inflammation on Plasma Nitrite Levels

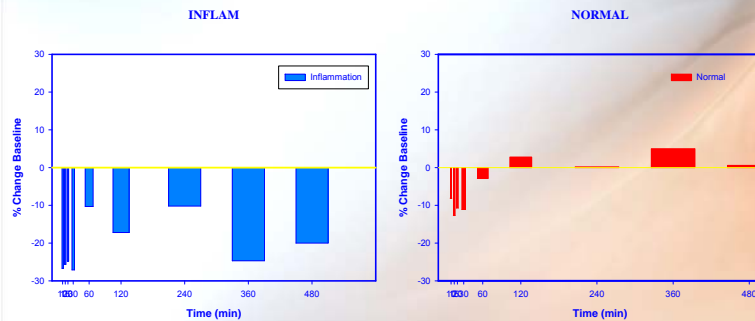


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## Summary of Dynamics Results

- The effect of the drug on blood pressure was more statistically significant ( $p < 0.05$ ) in the inflammation group compared to that of normal group.
- 3 folds reduction in the mean arterial pressure from baseline in the inflammation group compared to normal group.

### Effect of Oral Nifedipine on MAP changes with time in Normal and in rats under Acute Inflammation



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## Summary & Conclusions

- Large amounts of the drug escaped hepatic first-pass metabolism in the inflammation group.
- This can be attributed to inhibition of the first-pass metabolic processes (CYP<sub>450</sub> enzymes) in the liver responsible for low oral bioavailability of immediate release forms of NF
- NF plasma levels were reduced later possibly due to faster elimination rates through non-liver processes or due to the fact that the first order kinetics of NF elimination is enhanced by the presence of higher plasma concentration in rats with inflammation.



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- Inflammation has altered the hemodynamic and baroreflex mechanisms that regulate systemic blood pressure and prevents abnormal fluctuations in vivo.
- This effect of inflammation is supported by the fact that there is formation of large quantities of the vasodilator molecules nitric oxide over-balancing any opposing vasoconstrictors



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## Clinical Implications!

- These findings may indicate a second look at dosing for drugs similar to NF in patients who have inflammatory conditions.
- With the increase in plasma levels of NF, adverse events and toxicity are more likely to occur.
- Future studies involving larger number of rats are needed to fully investigate these issues



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## Questions?



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