THE TOXIC INTERACTION OF CALCIUM ANTAGONISM AND BETA BLOCKADE

Thesis

For the Master Degree in Clinical Toxicology

By

SIHAM MOSTAFA ALI EL-SHENWAY

National Organization for Drug Control and Research

Supervised by

PROF. DR.
ASSEM EL-HABASHY
Prof. of Forensic Medicine and Toxicology

PROF. DR.
LAILA MOHAMED EL-SIMARY
Prof. of Forensic Medicine and Toxicology

PROF. DR.
ADEL MAHMOUD KANDIL
Prof. of Pharmacology National Organization for Drug Control and Research

A. PROF. DR.
SAWSAN ABD EL-FATAH
Assistant Prof. of Forensic Medicine and Toxicology

FACULTY OF MEDICINE
AIN SHAMS UNIVERSITY
1990

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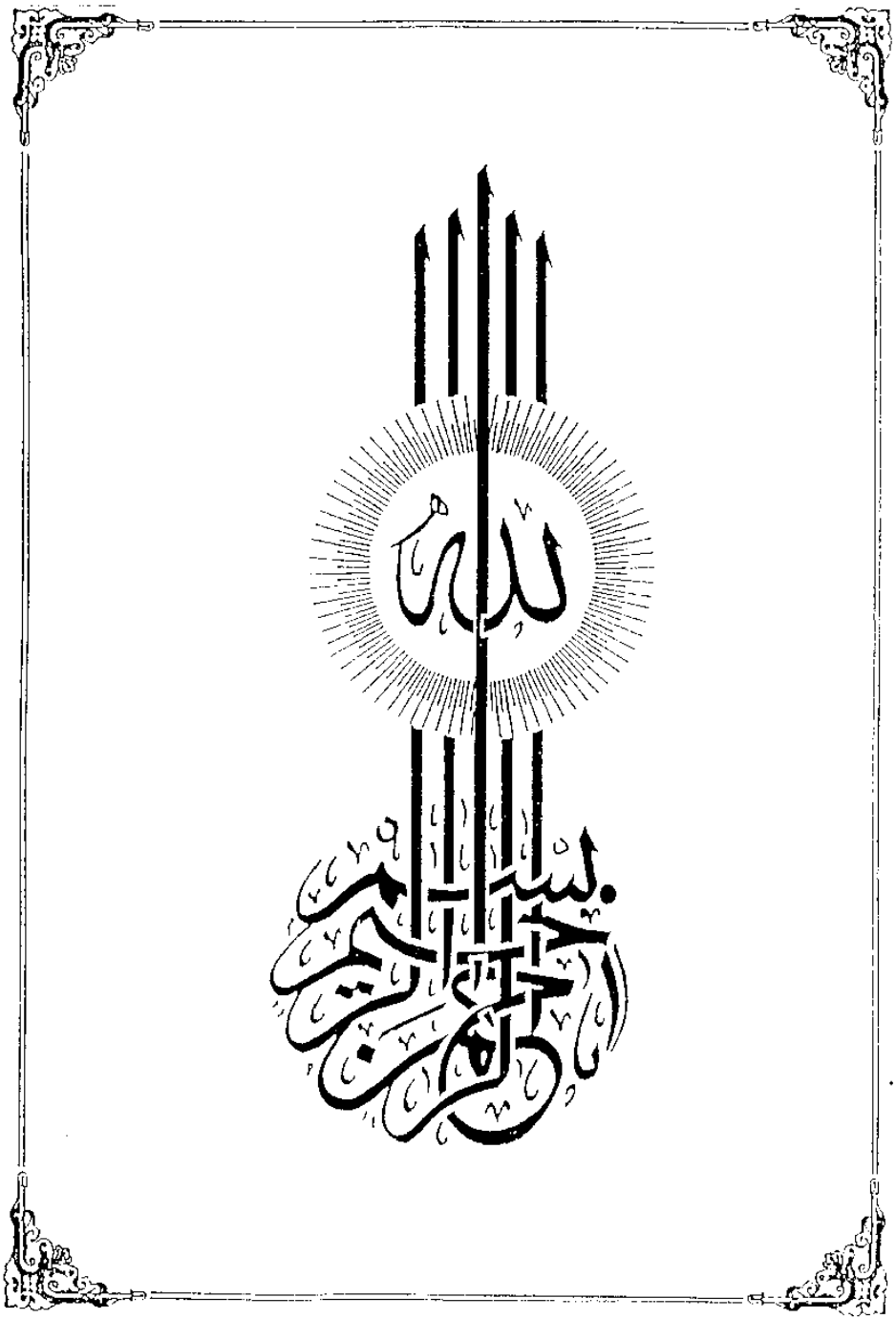

TO THE MEMORY OF MY BELOVED
FATHER AND BROTHER

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Introduction and Aim of Work

INTRODUCTION AND AIM OF WORK

The beta-blocking drugs have been well documented as safe and effective prophylactic therapy for exertional angina pectoris. Their primary effect is to reduce heart rate and the force of myocardial contraction through blocking of beta adrenoreceptors both at rest and during exercise (Frishman, 1983).

The calcium-entry blockers, although a relatively new class of therapeutic agents, have been in clinical use for more than 15 years in Europe (Storstein, 1985). Verapamil, the first to be introduced, was derived from papaverine, it is effective for the prophylactic treatment of stable exertional angina (Weiner and Klein, 1981).

The antianginal effect of the calcium-entry blockers is thought to be related to an increase in coronary and subendocardial blood flow and some reduction in myocardial oxygen demand through favorable effect on left ventricular after load (Daluz et al, 1980).

Thus, the calcium-entry blockers appear to alleviate angina by mechanisms different from the beta-blockers. In view of the different mechanisms of action, the combination

of these two types of agents might improve the hemodynamic profile, providing the potential for better control of symptoms of myocardial ischemia. At the same time, however, this type of combined therapy in the patient with ischemic heart disease could produce additive and potentially detrimental circulatory effects as the result of independent negative inotropic and chronotropic action of each agent. These potential concerns were supported by early clinical reports of hypotension and ventricular asystole when verapamil was administered to patients receiving a beta-blocker (Benaim, 1972 - Packer et al, 1982).

The combination of calcium channel blockers, such as verapamil with beta-blockers could have implications not only for angina pectoris and cardiac arrhythmia but also for hypertension (Doyle, 1983).

So, the interaction between these two groups of agents may cause problems (Opie and White, 1980 - Keival et al, 1982 - Packer et al, 1982 - Robson and Vishwanath, 1982).

This study is directed, firstly to review the pharmacotoxic effects of the two drugs, and secondly to demonstrate the toxicity of each compound in the experimental animals and their combination.

Review of Literature

REVIEW OF LITERATURE

I - Calcium antagonism :-

1) Historical evolution :-

The introduction of the calcium antagonists or calcium channel blocking agents represents the most exciting cardiovascular pharmacological advance in the past few years. These drugs of which verapamil, nifedipine and ditiliazem are the most clinically employed, have been used not only in the treatment of angina pectoris in Europe and Asia but also as chemical probes in the basic studies of the excitation secretion and excitation-contraction process (Schwartz, 1982).

The development of slow channel blockers dates to the early 1960. Linder (1960) observed that prenylamine, a newly developed coronary dilator, depressed cardiac performance in canine heart lung preparations.

Hass and Hartfelder in 1962 reported that verapamil, a coronary vasodilator, possessed negative inotropic and chronotropic effects that were not seen with others, apparently similar vasodilatory agents, such as nitroglycerin.

Fleckenstein et al (1967) suggested that the mechanism of action of these agents was not related to beta-adrenergic blockade, but to inhibition of the movement of calcium ions into cells.

Later, Fleckenstein (1970) specified that calcium antagonists acted by reversibly sealing specific calcium channels in the membrane of mammalian myocardial cell.

The name for this class of drugs remains controversial. Fleckenstein (1983) continues to favour the older term "calcium antagonist" and eschews the term "calcium blocker" because complete blockade of calcium influx via the slow inward current incompatible with life.

Katz et al (1984) suggested that the designation calcium antagonist is misleading because the drugs do not directly antagonize many effects of calcium on cellular processes. They are not calcium analogues.

Furthermore, the term calcium antagonist has also been applied to drugs that interfere with the activation of calmodulin by Ca^{++}, an effect that involves actions quite different from those produced when calcium influx across the plasma membrane is blocked. Because these drugs exert their effects primarily by inhibiting calcium entry into certain excitable cells, and certain non-excitable cells as well, the term " calcium entry blockers " has been proposed (*Van Houtte, 1981*).

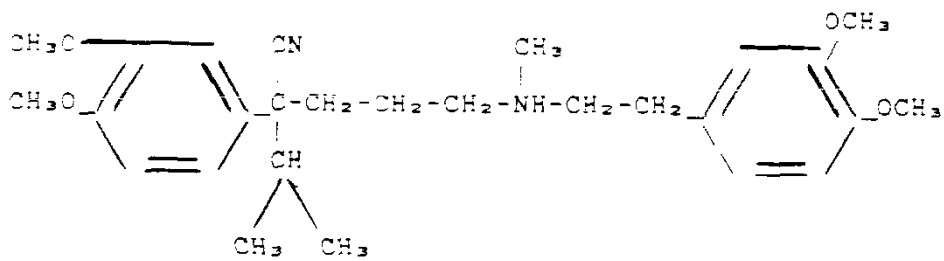
These drugs, however, do not block all of the mechanisms by which calcium can enter a cell; they do not for example block the sodium-calcium exchange *(Morad et al, 1982)*.

Their major action is to inhibit the passage of calcium through calcium selective channels in the plasma membrane of cardiac muscle, and other cells. Although the limited understanding of membrane structures has not yet provided a clear picture of these channels, it is believed that the most accurate description of these drugs is "blockers of calcium entry through a broad group of voltage-dependent and receptor-operated calcium selective plasma membrane ion channels" recognizing that the extent of this inhibition need not be complete.So, the "calcium channel blockers" is chosen as abbreviation of this definition *(Katz et al 1984)*.

VERAPAMIL

Verapamil, is a derivative of papaverine, was first used as a coronary vasodilator. Further studies showed that the drug has a novel mechanism of action : it blocks calcium channels in the membranes of the smooth and cardiac muscle cells (*Bigger and Hoffman, 1985*).

Chemistry :-



Verapamil after *Mannhold et al, 1978.*

Physical properties :-

Verapamil has a molecular weight of 491.08 almost white in colour, crystalline powder, practically odourless, with bitter taste (*Reynolds et al, 1989-a*).