PHARMACODYNAMIC EFFECTS OF CORGARD ON THE CARDIOVASCULAR SYSTEM IN EXPERIMENTAL ANIMALS AND POSSIBLE INTERACTIONS .

THESIS
Submitted in Partial Fulfilment
for Master Degree
(Pharmacology)

BY

ALAA EL- DIN MOHAMED SOLIMAN ABOU TALEB
M.B., B.Ch (December, 1979)
Demonestrator in Pharmacology Department
Faculty of Medicine Ain Shams University

Supervised By

Prof. Dr. SADIA ABDEL HAFIZE
Professor of Pharmacology

Dr. Zeinab M. Labib El- Gharib
Ass. Professor of Pharmacology

Dr. Gaber Abd El- Sabour Aly
Lecturer of Pharmacology

Faculty of Medicine
Ain Shams
University

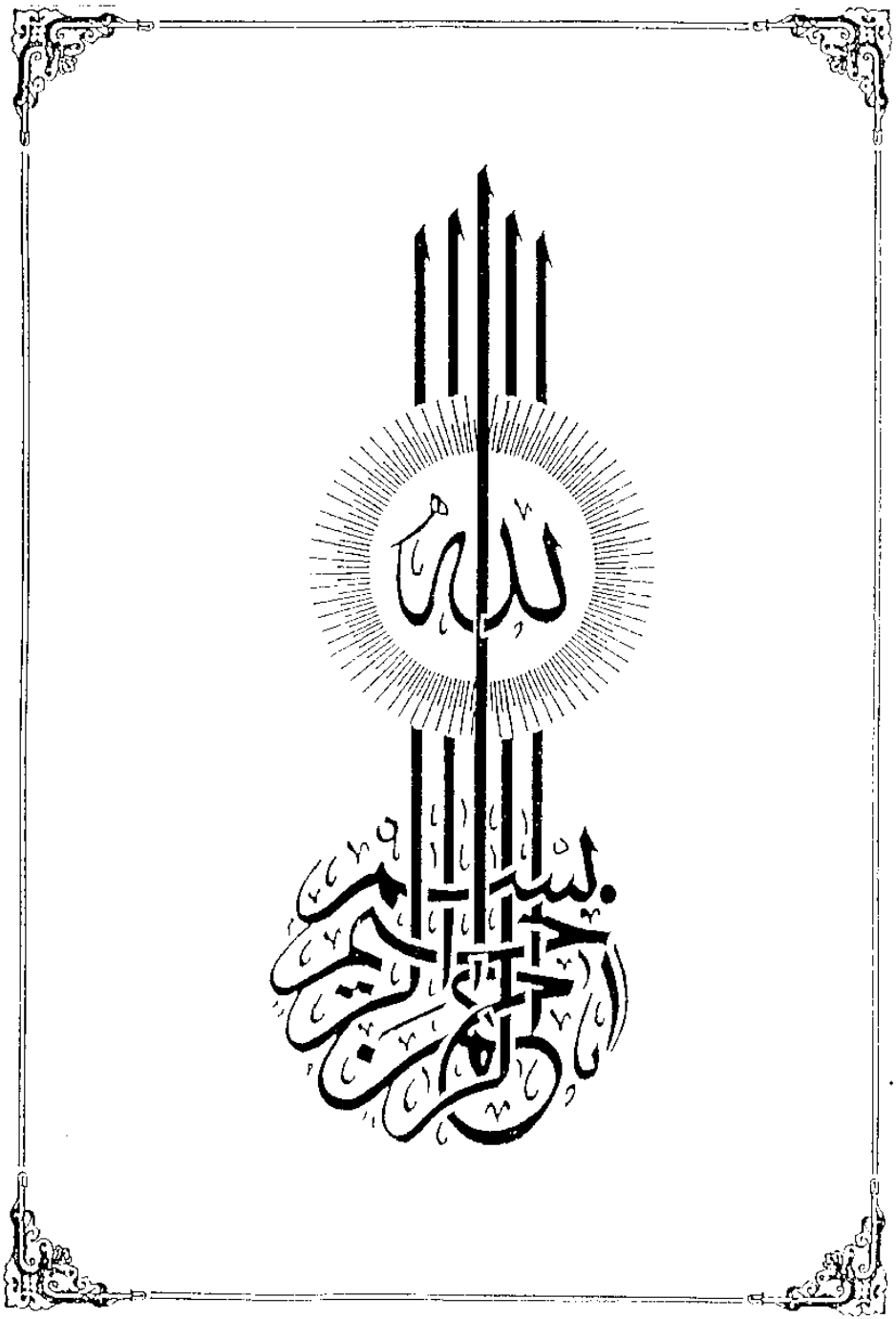
1984

بسم الله الرحمن الرحيم

« قالوا سبحانك لا علم لنا الا ماعلمتنا انك انت العليم الحكيم »

صدق الله العظيم

(سورة البقرة الآية ٣٢)



CONTENTS

ACKNOWLEDGEMENT

I would like to express my deepest appreciation and gratitude to my Professor Dr. Sadia Abdel Hafize, Professor of Pharmacology, Ain Shams University for her valuable supervision, guidance and encouragement. Her sincere help and stimulating suggestions have helped greatly in completing this work.

I wish also to acknowledge with my cordial thanks the precious and continuous support of Dr. Zeinab Labib El-Gharib, Assistant Professor of Pharmacology, Ain Shams University.

I owe a debt of gratitude to Dr. Gaber Abdel Sabour Aly, Lecturer of Pharmacology, Ain Shams University, who offered a valuable assistance and advices during performing the practical part of the study.

Dr. M. Kadry Madkour, Head of Pharmacological Research Laboratories, Cairo University, has kindly helped in the statistical analysis of this work. I am deeply indebted to his tremendous effort and guidance.

I am also thankfull to Dr. Ahmed Shaaban , Lecturer of Pharmacology, Ain Shams University for his helpful remarks and support.

INTRODUCTION

INTRODUCTION

During the last decade, beta blockers have established themselves as successful therapeutic agents in the management of angina, hypertension and certain types of arrhythmias (Frishmann et al., 1979). According to Hoffbrand, Shanks & Bricle (1976), ten years of propranolol high-lighted the broad ranging therapeutic applications of beta adrenergic receptor blockade.

Diseases of cardiovascular system, including cardiac arrhythmias, ischaemic heart disease and hypertension have proved to be particularly responsive to propranolol. Despite almost universal acceptance of propranolol and others in this pharmacological class of compounds, differences among the individual members of beta blockers have been sufficient to question the correctness of placing all compounds together, simply because they block the beta adrenergic receptors. In many instances, these differences are the results of attempts to improve propranolol (Prager, 1979).

According to Prager (1979) simplification of the dosage regimen is a primary objective that would provide a very significant patient benefit. In particular, an agent that

would satisfy all therapeutic objectives when given once daily would be ideal.

Nadolol, a new non cardioselective beta adrenergic receptor blocking drug, without partial agonistic activity or intrinsic sympathomimitic activity (Lee et al., 1975) or membrane stabilizing activity (Evan et al., 1976) was introduced lately. Its extremely long duration of action makes it suitable for once daily administration in both hypertension and angina pectoris.

The beta adrenoceptor blocking activity of nadolol has been demonstrated in various animal models (Lee et al., 1975; Lee and Baky, 1976 and Parham et al., 1977) it has been effective in once daily dose compared to propranolol given in a traditional regimen, four times daily (Heel et al., 1980). In addition, other specific principles of nadolol such as its excretion entirely in unmetabolised form, may offer advantages over other beta blocking drugs in specific patients. Unlike other beta blockers, nadolol has been shown to increase renal blood flow, but its relative effect on renal function under conditions of clinical usage, compared with other beta blockers, need further clarification.

In common with other beta blocking drugs, nadolol appears to decrease plasma renin activity in most patients

(Heel et al., 1980). However some properties such as lack of cardioselectivity may be disadvantageous.

The demonstration of at least two beta adrenergic receptors (Lands et al., 1967), the first B_1 receptors responsible for cardiac stimulation and lipolysis and the second B_2 receptors responsible for relaxation of vascular and bronchial smooth muscles and certain metabolic effects stimulated the search for agents that are cardiospecific, blocking only B_1 receptors.

The effects of catecholamines on contractile and electrical properties of the heart are mediated by beta adrenergic receptors, embedded in the sarcolemma. As determined by physiologic and radioligand binding studies, the large majority of myocardial beta adrenergic agonists are mediated predominantly, if not exclusively, by beta receptors (Watanabe, 1983). However, it has been suggested that chronotropy i.e. sinoatrial rate may be mediated by B_2 receptors located in the sinoatrial node (Carlsson et al., 1977).

Beta$_2$ adrenergic receptors are located on effector cells in proximity to adrenergic synapses, while B_1 receptors are located at some distance from the synapses (Wilffart et al., 1982). B_1 receptors appear to respond primarily to

neuronally released norepinephrine, whereas B_2 receptors respond preferentially to circulating epinephrine from adrenal medulla and to exogenously injected agonists. Moreover, as in case of alpha-adrenergic receptors, beta-adrenergic receptors located presynaptically on the nerve fibre regulate norephinephrine release. However, as opposed to presynaptic alpha receptors, which has an inhibitory role, stimulation of presynaptic beta receptors stimulates release of norepinephrine (Langer, 1981). Whereas ventricular receptors are exclusively $beta_1$ (Hedberg et al., 1980) approximately 25 per cent of atrial receptors are $beta_2$ subtypes. Atrial $beta_2$ receptors, presumably located within the sinoatrial node, may mediate the chronotropic effects of catecholamines on the heart.

It appears that catecholamines exert at least some of their effects through myocardial alpha-adrenergic receptors (Schumann, 1983). As with myocardial beta adrenergic receptors, stimulation of myocardial alpha receptors augments myocardial contractility (Coluci et al., 1982 and Lee et al., 1983).

The nature of the subtypes of myocardial alpha adrenergic receptors is somewhat controversial, although most evidence favours the presence of only $alpha_1$ receptors (Coluci et al.,

1983). A number of observations suggest that molecular mechanism by which alpha-adrenergic receptors exert a positive inotropic effect is different from that of beta receptors.

Wheras stimulation of beta-adrenergic receptors increases intracellular cyclic AMP, which is thought to mediate subsequent events, stimulation of alpha-adrenergic receptors has no effect on cyclic AMP production in the myocardium. Moreover, alpha receptor-mediated effects on inotropy are more sensitive to the extracellular concentration of (Ca^{++}) or blockade of (Ca^{++}) influx by calcium channel blockers than are beta-mediated effects (Braunwald, 1984).

Based on observations, it has been suggested that alpha-adrenergic receptors mediate an increase in inotropy almost exclusively by means of an increase in (Ca^{++}) influx (Wagner and Shuman, 1979).

Six beta blockers are already established in United states eg. atenolol, metoprolol, nadolol, pindolol, propranolol and timolol. They appear to be equally effective in the treatment of angina pectoris, but their differences in membrane stabilizing properties, lipo or hydrophelicity, cardioselectivity and intrinsic sympathomimitic activity affect the action of these compounds.

Several B-blockers have a powerful local anaesthetic action (ISA). In common with some local anaethetics, such as lignocaine, they exert a considerable anti-arrhythmic effect on the heart, especially exhibiting a quinidine-like effect in abolishing arrhythmias induced by ouabain (Dohadwalla, 1969).

In the absence of primary agonists (Norepinephrine, epinephrine), most B-blockers cause no cardiac response. However, others cause a measurable stimulatory response, indicating that they possess agonistic activity or intrinsic sympathomimitic activity (ISA). It has been reported that those drugs with intrinsic sympathomimitic activity can increase airways resistance and precipitate heart failure (Connolly, 1970 and Lyon, 1971).

The B-adrenoceptor blocking activity of nadolol has been demonstrated in various animal models (Lee et al., 1975; Lee and Baky, 1976). In vitro studies using guinea pig atrial muscle preparations, nadolol was about one third as potent as propranolol in blocking isoprenaline stimulation. However, in anaesthetized dogs and cats, intravenous nadolol was 2 : 4 times and 9 times, respectively, as potent as propranolol in blocking the heart rate and blood pressure responses to isoprenaline (Heel et al., 1980).

The duration of action of nadolol is 4 to 5 times longer than that of propranolol (Lee et al., 1975).

Many authors (eg. Evans et al., 1979) have suggested that nadolol has a much lower propensity to depress myocardial contractility than propranolol or many other B-blockers such as metoprolol, pindolol and oxprenolol eg. when large doses of nadolol were given to animals, possibly because of its lack of membrane-stabilizing activity, it showed less myocardial suppression. Moreover, in studies on man, nadolol may be less negatively inotropic when given to patients with incipient heart failure (Vukovich et al., 1979).

As with other B-blocking drugs, acute administration of nadolol in man increases systemic vascular resistance at rest. In anaesthetised dogs, both nadolol and propranolol increase diastolic coronary vascular resistance with a concurrent decrease in coronary blood flow (Heel et al., 1980).

Kern et al., (1983) have shown in patients with obstructive coronary diseases that the coronary vasoconstriction that normally occurs during the pressor test is intensified by beta adrenergic blockade with propranolol.

Bronchoconstriction results from blockade of B_2 receptors in the tracheobronchial tree, as a consequence, asthma and chronic asthmatic lung diseases are contraindications for the use of nadolol and other non-selective B-blockers. Since cardioselectivity is only relative, the use of such drugs (metaprolol and atenolol) in doses sufficient to prevent angina may still cause bronchoconstriction in susceptible patients.

Blockade of non cardiac (i.e. B_2) receptors inhibits catecholamine induced glycogenolysis and the vasodilatory effects of catecholamines in periphral blood vessels. Therefore, non cardioselective beta blockers may impair the defence of insulin induced hypoglycaemia, may precipitate episodes of Raynaud's phenomenon and may cause uncomfortable coldness of the distal extremities. Blockade of vasodilatory (B_2) receptors by non cardioselective beta blockers such as propranolol leaves the constrictive alpha adrenergic receptors unopposed and thereby enhances the vasoconstriction induced (Cruickshank, 1980).

The mechanism by which nadolol increases renal perfusion remains to be determined. One distinct possibility is that this agent is a direct renal vasodilator and that the blood flow increase does not reflect modification of an intrinsic

renal system. Experience with non specific vasodilators such as acetylcholine and dopamine has generally revealed a much longer increase in renal blood flow than was induced by nadolol. Secondly, the time course of the response to non specific vasodilators is typically different, in that a new steady-state course occurs within 3 minutes. A longer period was required for the renal vascular response to nadolol to reach a plateau, consistent with an indirect influence. Because the magnitude of the renal blood flow increase induced by angiotensin antagonists and converting enzyme inhibitors in man studies under similar circumstances, that is, with activation of the renin-angiotensin system by reducing sodium intake, it is tempting to implicate the fall in plasma renin activity as a responsible mechanism (Buhler et al., 1972).

The following table (1) shows the pharmacological properties of some B-blocking drugs, based on animal studies and in vitro models (after Brogden et al., 1977).