THE CARDIO TOXIC INTERACTION OF BETA-BLOCKERS AND AMINOGLYCOSIDES

Thesis

Submitted for partial fulfillment of the Master Degree in Clinical Toxicology

By

AZZA ABD EL RAOUF ZAGARY

National Organization for Drug Control & Research

Supervised By:

Prof. Dr. ASSEM EL HABASHY

Head of Dept. of Forensic Med. and Toxicology

Prof. Dr. LAILA MOHAMED EL SEMARY

Prof. of Forensic Med. and Toxicology

Dr. SAWSAN ABD EL FATTAH SHALABY

Assis. Prof. of Forensic Med. and Toxicology

Prof. ADEL MAHMOUD KANDIL

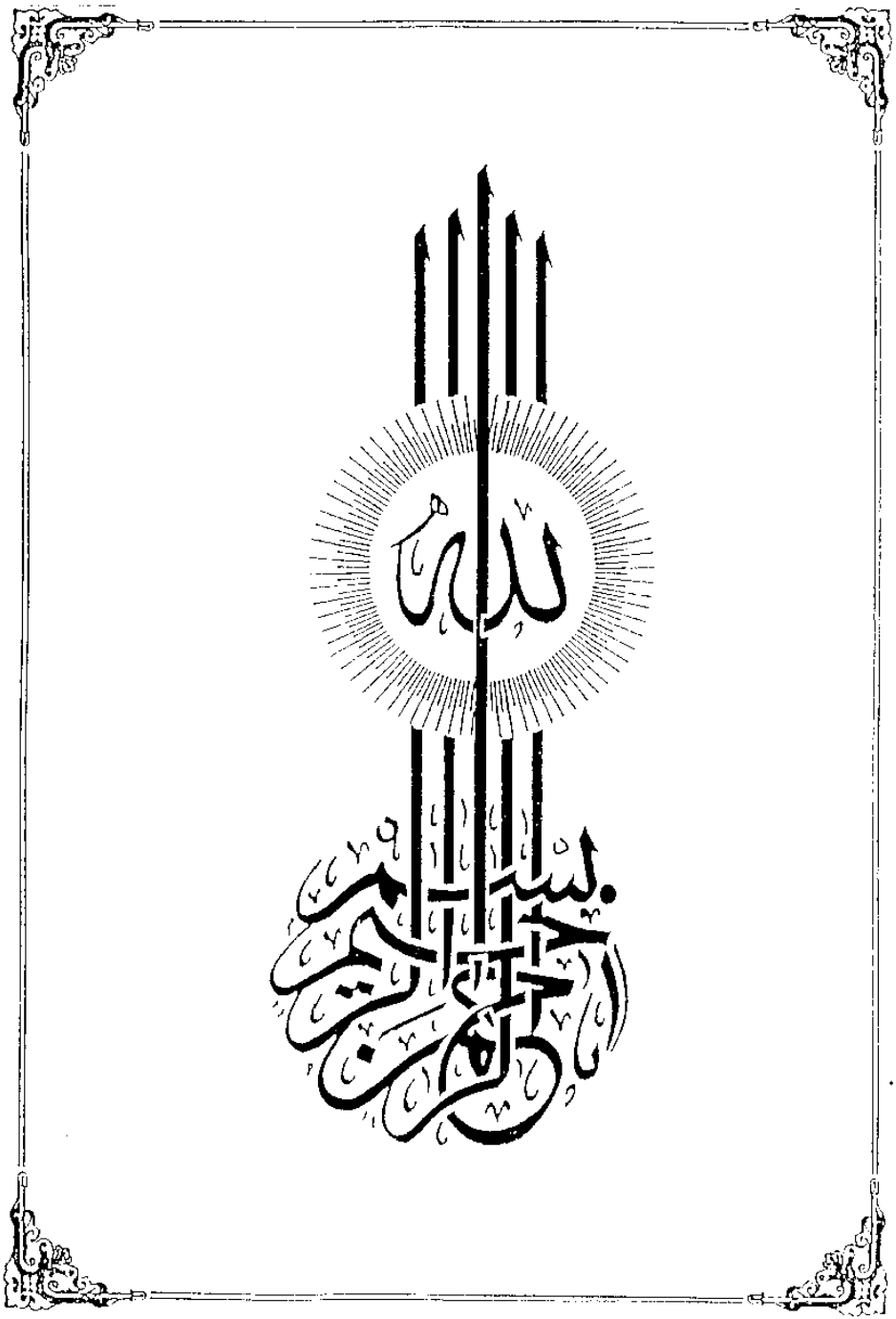
Prof. of Pharmacology

National Organization for Drug Control & Research

AIN SHAMS UNIVERSITY

FACULTY OF MEDICINE

1990



ACKNOWLEDGEMENT

I would like to express my sincere thanks and deepest gratitude to Prof. Dr. **Assem El Habashy**, *Head of Department of Forensic Med. and Toxicology Ain Shams University, for his valuable advice, guidance and continuous encouragement throughout the work.*

I wish to express my grief for the absence of my dear Prof. Dr. **Laila Mohamed El-Semary**, *Prof. of Forensic Medicine and Toxicology, Ain Shams University. Without her help and guidance, this work would have never been achieved. To her, I owe more than I can express.*

I am greatly indepted to Prof. Dr. **Sawsan Abd El-Fattah Shalaby** . *Ass. Prof. of Forensic Med. and Toxicology, Ain Shams University, for giving me the broad outlines of such subject and for her close supervision, useful suggestions and supportive guidance.*

I am greatly thankful to Prof. Dr. **Adel Mahmoud Kandil**, *Prof. of Pharmacology National Organization for Drug Control & Research, for his valuable criticism, support and helpful direction throughout this work.*

CONTENTS

AIM OF THE WORK

INTRODUCTION AND AIM OF THE WORK

Antimicrobial drugs and antiarrhythmic agents are widely used in medical practice. Many physicians prescribe drug combinations which are of different chemical and pharmacological nature. Such drug combinations may prove to be toxic to the patient.

B-blockers can precipitate heart failure in patients with reduced cardiac reserve. Also can produce heart block because they delay atrio-ventricular conduction (Weiner, 1985).

Aminoglycosides can produce myocarditis, palpitation, hypertension or hypotension, hypokalaemia or hyperkalaemia and hyponatraemia (Louis, 1987).

The historical, chemical and pharmacological profiles of test drugs will be documented. The toxicological effects of both drugs as well as their interaction will be stressed on accordance to their effects on the heart.

The aim of this work is to study in experimental animals the cardiotoxic effects of beta-blockers, aminoglycosides and their combinations.

REVIEW OF LITERATURE

CARDIOTOXIC INTERACTION OF B-BLOCKERS AND AMINOGLYCOSIDES

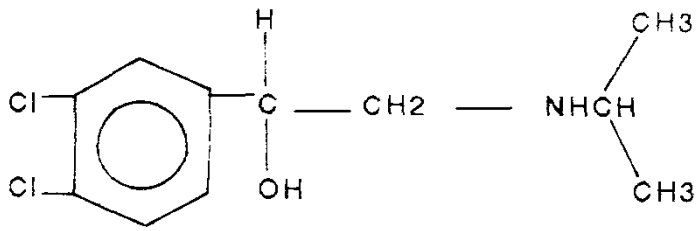
B-BLOCKERS (Propranolol):

History:-

The first drug shown to produce a selective blockade of B-adrenergic receptors was Dichloroisoproternol (DCT). but it was not used in man because it was a prominent B-receptor stimulant action. Pronethalol has weaker agonist properties and was used therapeutically, but it was replaced by propranolol which has a little or no agonist activity (Powell and Slater, 1958).

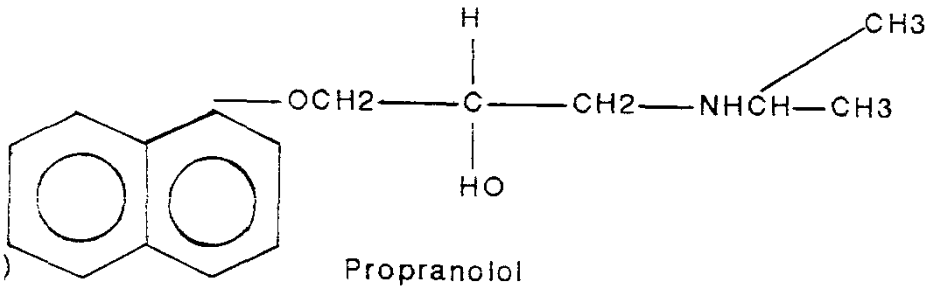
Chemistry:-

Most of the effective B-adrenergic blocking agents are derivatives of the B-receptor agonist isoproterenol (Fig. I, II)



(Fig. I) Dichloroisoproterenol (DCI)

(Weiner. 1985).



(Fig. II) Propranolol

(Weiner, 1985).

Pharmacokinetics:

Propranolol is well absorbed after oral administration. It is concentrated in the lung and to lesser extent in brain, liver, kidney and heart and is excreted in the urine after being almost completely metabolized. More than 90% of circulating propranolol is bound to plasma protein. The plasma half life in man is approximately 3 hours. Details of metabolic fate of propranolol are still not clear (Johnsson and Regardh, 1976).

Eight metabolites have been recovered from urine of dogs or man. One important metabolite is 4-hydroxypropranolol found only after oral or intravenous administration and also has blocking activity similar to that of propranolol (Oates, et al., 1977).

The metabolism of propranolol occurs mostly in the liver which has saturable, high affinity binding mechanism for the drug.

low concentration can be removed completely during a single passage (Evans, et al., 1973).

Pharmacodynamics:

B- receptor blockade has little effect on the normal heart with the subject at complete rest, but has profound effects when sympathetic control is high as during exercise. B-adrenergic antagonists without intrinsic sympathomimetic activity such as propranolol decrease heart rate, cardiac output, decrease the velocity of mechanical systole and slightly decrease the blood pressure in resting subject (Reynolds, et al., 1989).

Peripheral resistance is increased as a result of compensatory sympathetic reflexes, and blood flow to all tissues except the brain is reduced (Nies, et al., 1973).

The cardiac effects of B-adrenergic blockade are reflected in changes in Na^+ excretion. These effects on Na^+ excretion probably result from intrarenal haemodynamic changes that are part of the adjustment to the cardiac output. The magnitude of the effect appears to parallel the dependence of the heart on adrenergic stimulation to maintain adequate function. So in some patients with severe heart disease, B-adrenergic blockers

can cause progressive accumulation of Na^+, water, oedema and frank congestive heart failure (Nies, et al., 1971).

The effect of B-blockers is more marked under conditions of increased demand and sympathetic tone. Ventricular dimension and contractility are little affected in rest but during exercise, the decrease of end diastolic and end systolic ventricular size and increase myocardial contractility associated with exercise are reduced (Helfant, et al., 1971).

In patients with occlusive coronary arterial disease, propranolol can cause significant increase in ventricular end diastolic volume and pressure which leads to increase oxygen requirement also. Total coronary blood flow is reduced due to the decrease of end systolic pressure and heart rate. The reduction is mainly in subpericardial blood flow which leads to relative redistribution of flow, sc blcod flow to ischemic areas alters less than other regions (Pitt and Craven, 1970).

The Effect Of Propranolol On Blood Pressure:

Propranolol is an effective antihypertensive by several mechanisms:-

1- Reduction of cardiac output.

2- B-adrenergic agonists are known to increase the release of norepinephrine from adrenergic nerve terminals propranolol blocks this effect (Dixon, et al., 1979).

3- B_2 adrenergic agonists are known to stimulate the release of renin from the juxta glomerular apparatus, propranolol blocks this effect (Oates. et al., 1977).

4- Also reduce but don't completely block the increase in plasma renin activity induced by Na deprivation (Michelakis and Mcallister, 1977). Chronic treatment of hypertensive patients with B-Blockers result in a slowly developing reduction in blood pressure (Simpson, 1980).

The Effect Of Propranolol On Arrhythmia:-

1- Automaticity: B- adrenergic blocker (propranolol) decreases the slope of phase 4 depolarization so decreases automaticity of S-A node, A-V node and Purkinje fibres (Shand, 1975).

2- Excitability and threshold:-

The electrical threshold of atria and ventricles is not much affected by propranolol (Wallace, et al., 1967).

3- Responsiveness and conduction:

Only very high concentration of propranolol (1000 to 3000 ng/ml.) affect responsiveness in purkinje fibres so concentration over 1000 ng/ml are required for control of ventricular arrhythmias (Davis and Temte, 1968).

4- Duration of action potential and refractoriness:-

Propranolol has little effect on the duration of action potential in sinus node, atrium or A-V node. In ventricular muscle action potential shortens slightly. in Purkinje fibres action potential often shortens substantially (Shand, 1975).

Propranolol has a little effect on refractoriness of normal atrial or ventricular muscle. It causes s substantial increase in the effective refractory period (ERP) of the A-V node due to its B-adrenergic blocking action, this action is the basis of the major uses of propranolol as an antiarrhythmic drug. Also effective refractory period (ERP) of Purkinje fibres is shortened substantially (Weiner, 1985).

5- The effect of propranolol on reentrant arrhythmias:-

In paroxysmal supraventricular tachycardia due to A-V nodal reentry, the substantial increase in A-V node refractoriness may abolish reentry. In the ventricles propranolol has quinidine like