HAEMODYNAMIC STUDY ON A NEW AJMALINE DERIVATIVE (NEO GILURYTMAL)

THESIS

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BY

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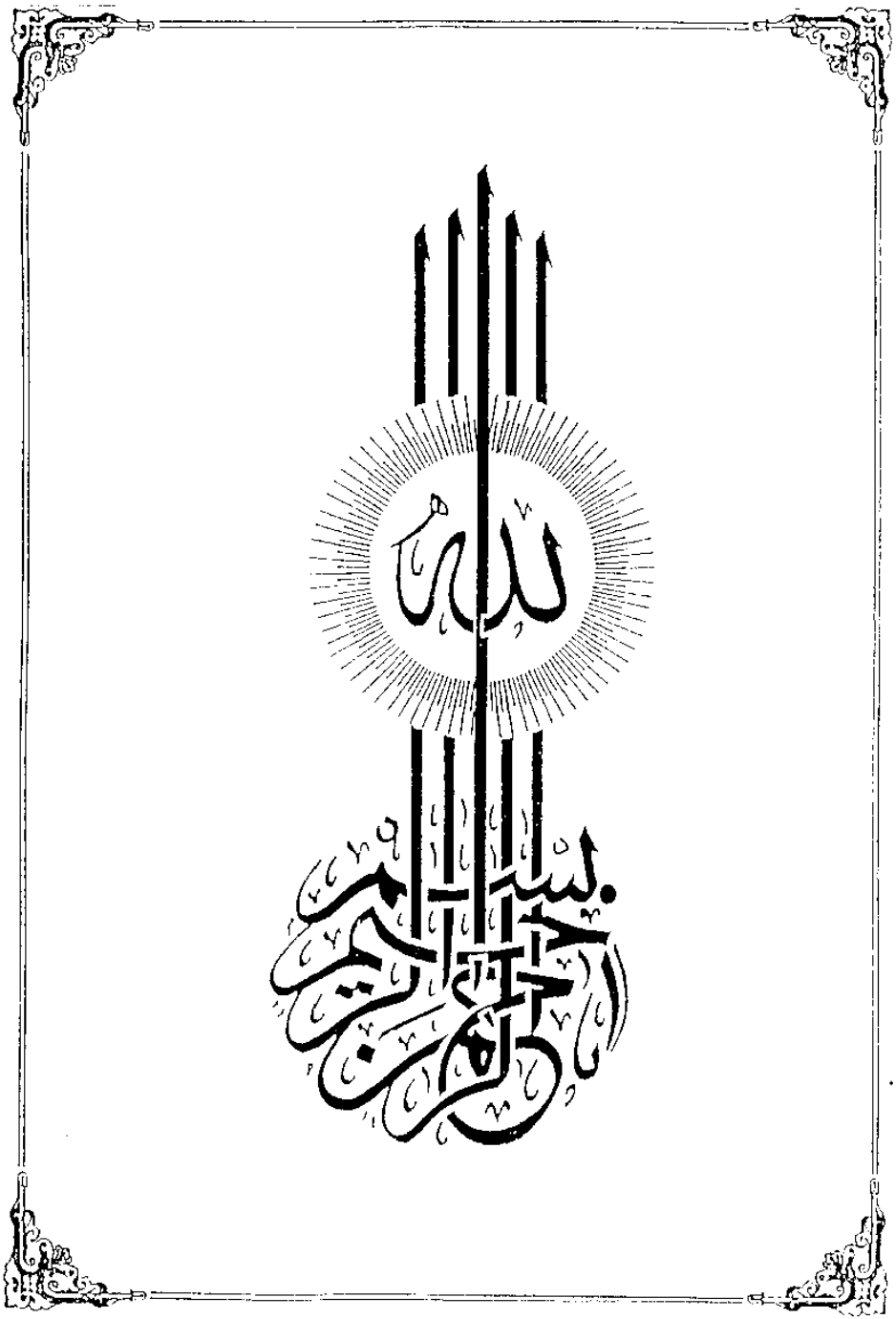

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C O N T E N T S

INTRODUCTION

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Cardiac dysrrhythmia causing sudden death is a serious worldwide public health problem (Somberg, 1984).

Dysrrhythmias are harmful to the extent that they reduce the cardiac output, decrease the blood pressure and interfere with the perfusion of the vital territories of the brain, heart and kidney (Maurice and Barry, 1988).

To prevent tachycardiac dysrrhythmias and subsequent sudden death, antiarrhythmic drug efficacy must be accurately evaluated, so that they become very useful in a patient whose life becomes threatened by such dysrrhythmias (Somberg, 1984).

A high degree of effectiveness combined with a low level of toxicity and a prolonged antiarrhythmic action are the aims of new antiarrhythmic substances (Schwartz-Kopff et al., 1983).

The frequent use of the available antiarrhythmic drugs predisposes to worsening of the existing cardiac dysrrhythmias (Torres et al., 1985).

It is known that most antiarrhythmic drugs have a relatively low therapeutic index. They often produce

intolerable side effects. Therefore, it is important to understand both the pharmacokinetic and pharmacodynamic characteristics of these drugs in order to use them judiciously in the treatment of cardiac dysrrhythmias (Hashimoto et al., 1986).

Sometimes, it is useful to use a combination of antiarrhythmic drugs with different pharmacological actions to overcome the refractoriness as well as to reduce the side effects. Therefore, the introduction of agents which are more effective with fewer side effects is very important when one is confronted with a multitude of such drugs (Somberg, 1984).

It is essential to classify antiarrhythmic agents into groups to determine the efficacy and toxicity of these agents and to detect the appropriate combination therapy for refractory dysrrhythmias. The most useful classification is based on the dominant electro-physiologic properties of each agent. This is known as Vaughan William classification (Richard et al., 1986).

Ajmaline, is an alkaloid derived from the Indian plant Rauwolfia serpentina which was tried in experimental and clinical atrial and ventricular dysrrhythmias (Bojorges et al., 1974).

The Rauwolfia serpentina alkaloid have a number of pharmacological properties. Five alkaloids had been isolated from the roots of this plant, and were divided into 2 groups: (1) A reserpine group, and (2) ajmaline group (Bazika et al., 1966).

Ajmaline in contrast to reserpine does not affect the peripheral nerves or central nervous system (Bojorges et al., 1974).

In addition, ajamline has neither the sedative, the hypnotic nor the tranquilizing effect of Rauwolfia serpentina (Khalilullah et al., 1980).

There are different types of Rauwolfia which include Rauwolfia serpentina, Rauwolfia caffra sand and Rauwolfia salicifolia. They were used clinically in chronic hypertension (Carvajal et al., 1986).

Ajmaline exerts its antiarrhythmic effect by depressing the intraventricular conduction and by prolonging the refractory period. This suggests that the direct action of the drug on the heart is assigned to its anticholinergic effect (Bojorges et al., 1974).

The antiarrhythmic action of ajmaline is satisfactory only after parentral administration. Since no

metabolites of ajmaline were detected in the serum samples, it seems that no biotransformation of the drug takes place either during absorption from the gastro-intestinal tract or after it reaches the liver (Antilla et al., 1978).

The absorption of ajmaline is influenced by many factors including age, hepatic diseases and associated drug intake (Daquet, 1982).

It is measured in the blood and tissue homogenate using specific reverse high phase performance liquid chromatography (Hori et al., 1984).

The drug is equally distributed in the atrial and ventricular tissues with equal concentrations and causes a decrease in the conduction rates in both sites with equal intensity as evidenced by the fact that there are equal changes in the PQ and QRS complexes (Yaushara et al., 1987).

The suppression of intraventricular conduction caused by ajmaline is remarkable but it has a brief duration (Chiale et al., 1982).

Ajmaline is an effective drug in the treatment of serious toxic digitalis dysrrhythmias. This is mediated

by decreasing the rate of conduction in the myocardium, prolonging the repolarization period and by altering the cell membrane permeability to Na^+ and K^+ and also by increasing the catecholamine content of the myocardium (Bazika et al., 1966).

It is also used in the management of acute atrial flutter and fibrillation with a fast ventricular response in patients with Wolff-Parkinson White syndrome. The aim of the treatment is reduction of the ventricular rate to avoid the development of the life threatening ventricular fibrillation (Sclarovsky et al., 1980).

Ajmaline also is effective in the treatment of acute ventricular tachycardia, and can replace electric shock (Manz and Luderitz, 1986).

Normalization of QRS complex (loss of prexcitation) is seen after intravenous administration of the drug. However, this effect is not durable (Khalilullah et al., 1980).

The drug also can be used as a diagnostic agent since its administration causes the reappearance of bundle branch block. This demonstrates the great sensitivity of ajmaline test for detecting subclinical

or the undetected form of fasicular damage. In patients with chagas disease which is caused by trypansoma cruzi infestation, administration of ajmaline can induced vertricular extrasystoles and an injury current (marked ST segment elevation), and it can evoke typical electro cardiographic changes characteristic of chronic chagasic myocarditis in patients showing no signs or early minor non specific signs of myocardial involvement (Chiale et al., 1982).

Ajmaline may reveal sinoatrial block. It can be used to diagnose atrioventricular block by increasing the atrioventricular conduction in patients with supra-hisian A-V block (Perrot et al., 1982).

The use of large doses of ajmaline may be complicated by serious complications such as remarkable depression of conduction, severe hypotension and decrease in the myocardial contractility (Bojorges et al., 1974).

The drug may cause neurological manifestations in the form of eye twitchings, convulsions, respiratory depression, hepatic cholestasis as well as agranulocytosis, but these effects do not appear except at higher doses (Somberg, 1984).

Wegehaupt and Hager (1970) reported that one of the problems of using oral ajmaline is that its safety margin is very narrow so that gastrointestinal distress and circulatory complications may develop with even the therapeutic doses. Thus, it become apparent that modification of the chemical structure of ajmaline must be studied in order to eliminate its unpleasant effects without lossing its desired properties.

N-propyl ajmaline bitartarate, the oral anti-arrhythmic drug derived from ajamline, was found to possess a higher lipid solubility. Thus, it easily penetrates the blood brain barrier and reaches the central nervous system (Iven, 1977).

It is synthesized from Rauwolfia alkalcid ajmaline with the addition of propyl group (Bussmann, 1978).

N propyl ajmaline bitartarate is a recently introduced antiarrhythmic drug. The main advantage of this agent over the original drug ajamline is that it is rapidly and completely absorbed from

the gastrointestinal tract and its therapeutic activity is maintained for longer period (Bussmann, 1980).

The synthesis has been performed by Buchler by means of reaction of (I - C^{14}) - propyl iodide with ajmaline. The radiochemical purity had been checked by thin layer chromatography on silica gel plate. The drug is strongly bound to plasma proteins when used in 2 concentrations the following data were obtained

223 ng/ml : 60.9 ± 0.9 %

446 ng/ml : 61.2 ± 1.3 %

This means that about 40 percent of the active substance is always present in the plasma in an available form. Following oral administration of carbon labelled N - propyl ajmaline bitartarate, 6 metabolites were detected in the urine. Three main metabolites result from simple hydroxylation at carbons 3, 5, 14 or 21. Another metabolic pathway appears to be the oxidation of indole structure or even the hydroxylation of the lateral propyl group (Hausleiter et al., 1982).

In an earlier work, Schaumnloffel (1975) and Spilker et al., (1975) showed that the elimination half life of prajmalium bitartarate differs according to the species of the animal used. It was found to be 10-12 hours in the rat, and about 15-18 hours in man, but it is only 4 hours in dogs.

Raschack (1975) observed that following the intravenous infusion in dogs, N-propyl ajmaline bitartarate was approximately 10 times more potent than ajmaline.

The results may be due to slower elimination of the drug. The elimination of radioactivity occured at an average total clearance of approximately 60 ml/minute with a half life of 29-33 hours. This corresponds to elimination half life of approximately 6 hours of unaltered N-propyl ajmaline bitartarate (Nieminen et al., 1978).

At the present time, there is no definite analytical method for the determination of the plasma therapeutic concentrations of N-propyl ajmaline bitartarate in order to study the