SCREENING OF COMMON ANTIHYPERTENSIVES FOR A POTENTIAL ATHEROGENIC EFFECT

THESIS

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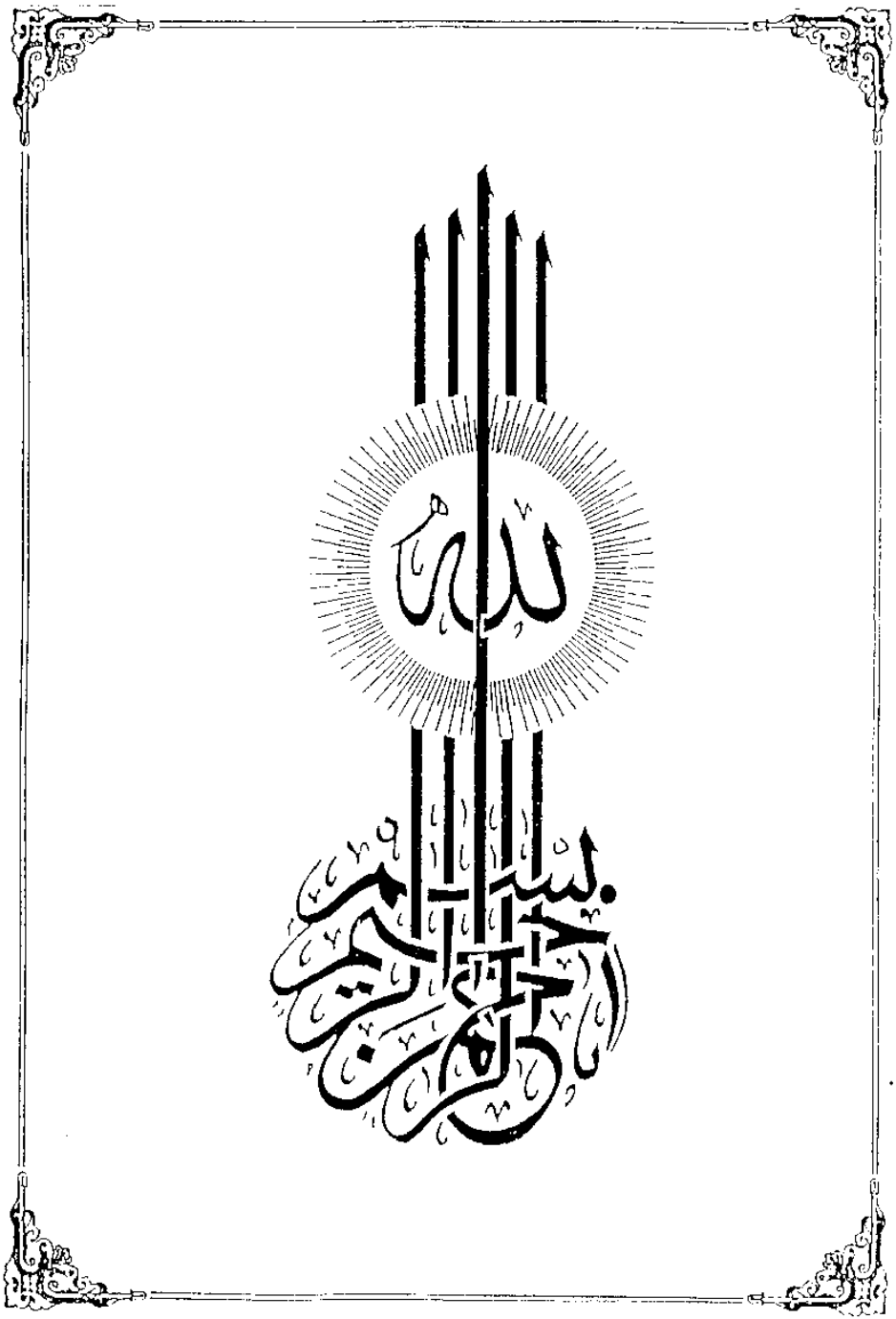

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C O N T E N T S

INTRODUCTION
and
AIM OF THE WORK

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Few reports indicated that treatment with diuretics as well as beta-adrenoceptor blockers in hypertension may significantly alter lipoprotein pattern (Gluck et al., 1978_a and Helgeland et al., 1978_a) .

In view of the postulated association of plasma lipid changes and cardiovascular disease and because these changes may be long-lasting and may cancel part of the potential benefit of blood pressure control in mildly-hypertensive patients, it seemed of utmost importance to screen, experimentally, some of the clinically-useful antihypertensive agents for such a potential effect and this is the aim of the present work . In addition, this work is planned to investigate the possible mechanisms underlying this potential action .

* The drugs proposed for screening are :

1. Beta blockers : propranolol (non-cardioselective), atenolol (cardioselective) and labetalol (alpha- and beta-blocker) .

2. Diuretics : Hydrochlorothiazide, frusemide and chlorthalidone .

* Experiments are conducted on rats for the following :

1. Effect of long-term treatment (12 weeks) on lipid metabolism in the serum as regards :

   a. Total lipids .

   b. Triglycerides .

   c. Total cholesterol .

   d. High-density lipoprotein-cholesterol (HDL-cholesterol).

   e. Low-density lipoprotein-cholesterol (LDL-cholesterol).

   f. Also, urate estimation is suggested .

2. In addition, blood pressure is recorded to see how changes in lipid pattern would correlate with blood pressure measurements .

3. Effect of long-term treatment on the microscopic structure of rat heart, liver and blood vessels , especially the aorta as shown by light microscopy .

Atherosclerosis was induced by repeated vitamin-D administration , according to the method of Baraka et al. (1980) , in a trial to compare the pathological lesions that may be induced under the effect of the drugs tested with the full blond picture of atherosclerosis, induced by vitamin-D administration .

* To investigate the possible mechanism for these potential changes, the following is planned for :

1. Estimation of glycosylated haemoglobin as a reflection of changes in serum glucose level, because of the possibility that changes in lipid pattern might be secondary to the effect of the drugs, under investigation, on insulin action or release .

2. Estimation of packed cell volume (haematocrite value) as an index for changes in the extra-cellular fluid volume .

REVIEW OF LITERATURE

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C H A P T E R (I)

Plasma Lipid Changes During Antihypertensive Therapy

The benefit of any medical intervention, particularly drug therapy, must be weighed against its cost . These costs are not only money expenditure , but also effects on lifestyle and ovarall health (Mc Carron, 1984) .

Because many studies have demonstrated that blood pressure levels alone are insufficient to assess either the need for therapy or the adequacy of the outcome once the goal blood pressure is achieved (Alderman and Madhaven, 1981 and Freis, 1982), the physician's responsibility is to incorporate strategies that not only normalize the blood pressure, but also reduce the exposure of the patient to the hidden cost (Slason and Weinstein, 1977) .

In simple terms, interventions that are intended to decrease blood pressure, are prescribed for patients with, or at risk of developing, hypertensive cardiovascular disease. The implied purpose is that by doing so, each patient will be at some reduced risk of developing premature cardiovascular

complications , including coronary heart disease and cerebrovascular disease . In applying such therapy , costs must be acceptable , including modification of other risk factors that could cancel any possible benefit from lowering of the blood pressure (Mc Carron, 1984) .

It has been convincingly demonstrated that life expectancy is inversely related to blood pressure (Miall and Chinn, 1974) . Similarly, it seems well established that the increased risks of cerebrovascular accidents and of cardiac or renal failure are reduced by sustained control of hypertension (Veterans Administration Co-operative Study Group on Antihypertensive Agents , 1970) . The effects of antihypertensive treatment upon the development of atherosclerosis and particularly coronary artery disease are less well defined . Earlier studies showed no reduced frequency of death from coronary artery disease in treated hypertensives, and suggested that beneficial effects were selective for hypertensive complications other than coronary artery disease (Breckenridge et al., 1970). However, more recent studies of mild hypertension suggested that the risks of coronary artery disease are also reduced by treatment of hypertension (Hypertension Detection and Follow-up Program Cooperative Group, 1979 and Management Committee, 1980) . One possible explanation for these

differences is that other coronary risk factors may be adversely affected by some agents which lower the blood pressure . Antihypertensive treatment regimens which produce comparable blood pressure control could have different effects upon the development of coronary artery disease (Hulley et al., 1980) . In view of this controversy , it seems a must to review and to study the effects of some antihypertensive agents e.g. beta-blockers and diuretics, on plasma lipids and hence their potential atherogenicity .

Effects of Beta-blockers :

Epinephrine and norepinephrine mediate metabolic effects through stimulation of alpha- and beta-adrenergic receptors; therefore, drugs which either stimulate or inhibit adrenergic receptors should be expected to affect both glucose and lipid metabolism (Ahlquist, 1948; Lands et al., 1967 ; Day, 1975 and Carruthers, 1979) .

As antagonists to beta-adrenoceptors have progressively gained acceptance as valuable agents in the control of hypertension, angina and some types of cardiac arrhythmia , increasing reports of their capacity to change plasma lipids and lipoprotein patterns have appeared (Johnson , 1982) .

At least, eight different beta-blockers have been examined with different characteristics as regards alpha-antagonism, cardioselectivity, partial agonism and membrane stabilization. Most systematic studies have been of propranolol and the relatively cardioselective ($beta_1$) blocking agent metoprolol, with reasonably systematic studies of other agents as atenolol, labetalol, nadolol, oxprenolol, pindolol and practolol .

Lloyd-Mostyn et al. (1971) performed a crossover study in twelve patients with either ischaemic heart disease or hypertension , using propranolol (160 mg/day) and practolol (200 mg/day) . Treatment was continued for 14-day periods with a 14-day intervening control period . Subsequently, all patients were treated for another period with oxprenolol (160 mg/day) . All were selected on the basis of pre-existing elevation of total cholesterol above 250 mg/dl , or of triglycerides above 150 mg/dl . Changes in triglycerides were very variable, and therefore not significant . There was some tendency for mean levels of triglycerides to rise from 202 to 262 mg/dl on propranolol , from 213 to 229 mg/dl on practolol, and to be unchanged with oxprenolol (178 to 184 mg/dl) . Total cholesterol appeared unchanged by any of the three beta-blockers .

Barboriak and Friedberg (1973) studied the effect of propranolol in doses of 40 to 160 mg/day, for two weeks, in fourteen subjects, including five patients with angina, four with paroxysmal tachycardia and five normal volunteers. By comparison with pretreatment values, there was an apparent, though non-significant, elevation in triglycerides from 170 to 212 mg/dl . There was no trend for changes in total cholesterol .

Thirty-nine patients with myocardial infarction were randomly assigned by Ghosh et al. (1975) to parallel treatment groups of practolol (400 mg/day) or placebo . In this double-blind study, twenty received active and nineteen received placebo treatment . Ages ranged from 34 to 68 years . No baseline values were obtained, and no significant differences in either total cholesterol or triglycerides were seen at one, three or six months of treatment.

Tanaka et al. (1976) studied five men and five women with hemiplegia as in-patients . All have relatively normal fasting cholesterol and triglycerides . After four weeks off all drugs, two baseline blood samples were obtained, and 60 mg of propranolol given per day for seven weeks with the dose being doubled for the final week . There was a trend for mean triglycerides to increase from 113 to 135 mg / dl