OXPRENOLOL, METHYLDOPA AND LIPIDS IN DIABETES MELLITUS

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- 1 Twelve-week courses of oxprenolol and methyldopa were administered in a randomised, double-blind cross over study to ten insulin dependent hypertensive diabetics.
- 2 Prior to treatment, and at the end of each period of drug administration, fasting levels of high density lipoprotein, triglycerides, free fatty acids and cholesterol were measured.
- 3 Neither preparation altered levels of high density lipoprotein and cholesterol, but both drugs significantly reduced the free fatty acids.
- 4 Whereas oxprenolol did not alter triglyceride levels, methyldopa significantly elevated triglycerides above pre-treatment values.
- 5 Oxprenolol does not appear to influence lipoprotein fractions affecting the relative risks of coronary heart disease, but methyldopa seems to have potentially detrimental effects of triglyceride levels.

Introduction

Administration of β -adrenoceptor blocking agents for prolonged periods has been shown to be associated with alterations in serum lipids. The most frequently observed changes have been reduced levels of high density lipoprotein (HDL) (Tanaka *et al.*, 1976; Leren *et al.*, 1980), increased levels of triglycerides (Waal-Manning & Simpson, 1977; Shaw *et al.*, 1978), and variable changes in free fatty acid levels (FFA) (Tanaka *et al.*, 1976; Day *et al.*, 1979). Such alterations are thought to constitute an increased risk of coronary heart disease (CHD) in addition to that of hypertension, the impetus for administration of such drugs. Another risk factor for CHD is diabetes mellitus, a common disorder, thus raising therapeutic problems in those patients who have this illness co-existing with raised blood pressure.

Oxprenolol is a long established β -adrenoceptor blocker. In an attempt to assess its suitability in diabetic hypertensives a study was undertaken to compare its influence on serum lipids with that of another widely used hypotensive agent, methyldopa.

Methods

Ten insulin-dependent diabetics with stable diastolic blood pressures between 100 and 200 mmHg entered and completed a randomised, double-blind, cross-

over study. They were not receiving any hypotensive medication on entry to the trial, and there was no detectable renal or cardiovascular disease. Each patient received a 12 week course of oxprenolol (up to 160 mg twice daily) and methyldopa (up to 500 mg three times a day) administered in identical capsules given in random order, separated by a 4 week wash-out period of placebo capsules, of identical appearance to the active agents. The capsules were dispensed in three containers, clearly marked for morning, afternoon and evening consumption. The middle container of the oxprenolol course contained placebo capsules, thus avoiding identification of the two agents. The patients were seen at intervals of 2 weeks when blood pressure was recorded using a Hawksley Random Zero sphygmomanometer following 10 min rest in a sitting position. Any adverse drug effects were recorded after open ended questioning and diabetic control was reviewed. Each patient's diet was kept constant, although minor adjustments of insulin dosage were routinely undertaken, such as when variations in physical activity occurred. Drug compliance was checked by counting the remaining capsules in each of the three containers.

Blood samples were taken in a fasting state, one of us (GFAB) visiting the patients' homes prior to breakfast and the administration of any medication. Samples were taken prior to the beginning of the courses of treatment and at the end of each period of medication. Serum was assayed for cholesterol (cholesterol esterase/oxidase method, Boehringer

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126055), HDL (enzymatic cholesteroid), triglycerides (Cal Biochem, Triglyceride Stat-pak 869262) and FFA (Boehringer 126055). Electrolytes, urea, creatinine and glucose were measured in the same samples. The analytical methods for lipoprotein assay were not known to be affected by the presence of either oxprenolol or methyldopa.

Comparison of lipid fractions, glucose, and other biochemical parameters at each stage of the trial was undertaken using paired sample Students' *t*-tests.

Results

The ten patients who participated in the trial had a mean age of 48 years (range 22–65), and a mean weight of 76 kg (range 64–82). Table 1 summarises the overall serum lipid levels during the specified periods of the trial and also the blood pressure readings with significant falls in blood pressure being achieved by both hypotensive agents. The HDL levels remained low throughout the study (normal range 0.8–2.0 mmol/l), and were not altered significantly by either oxprenolol or methyldopa. Similarly, the serum levels of cholesterol and glucose remained unchanged from pretreatment values. Oxprenolol was found to exert no significant effect on triglyceride levels, but values were significantly raised during the period when methyldopa was taken ($P < 0.01$), and this occurred in all patients.

Both oxprenolol and methyldopa ($P < 0.05$) reduced FFA markedly from pretreatment levels which had been high (normal range 0.09–0.6 mmol/l), to normal values. Variations in levels of fasting blood

glucose were noted, but no correlation was found between these differences, and any changes in the various lipid fractions. There were no significant alterations in levels of urea, creatinine and potassium.

When the patients receiving oxprenolol first (five patients) were compared as a group to those receiving methyldopa initially (five patients), no significant differences between the various lipoprotein fractions could be demonstrated, indicating that not only were the patients satisfactorily randomised, but also that the washout period was probably adequate.

Discussion

The risk of CHD in individuals is increased in the presence of certain well documented metabolic abnormalities, notably, increased levels of cholesterol (Keys, 1970; Pooling Project Research Group, 1978), and raised levels of triglycerides when they exceed 1.7 mmol/l (Pelkonen *et al.*, 1977). The evidence establishing cholesterol as a risk factor is better established than that linking triglycerides, but some large prospective studies (Carlson & Bottiger, 1972; Pelkonen *et al.*, 1977), have demonstrated an independent association of these two lipid fractions with an increased cardiovascular mortality. Recent reports (Miller & Miller, 1975; Enger *et al.*, 1979), have drawn attention to the HDL fraction and its inverse correlation with CHD; a high risk being associated with low levels of this lipoprotein. Studies have revealed that these alterations in the various plasma lipoproteins are widespread in patients with diabetes mellitus, even in the absence of CHD (Corn-

Table 1 Details of serum lipid fractions prior to treatment and at the end of both periods of anti-hypertensive therapy (mean $\pm$ s.e. mean) with blood pressure and pulse rate (mean $\pm$ s.e. mean) recorded before, and during medication.

	Pre-treatment	Oxprenolol	Methyldopa
HDL (mmol/l)	0.91 $\pm$ 0.08	0.88 $\pm$ 0.06	0.88 $\pm$ 0.09
Triglycerides (mmol/l)	1.18 $\pm$ 0.08	1.08 $\pm$ 0.1	1.50 $\pm$ 0.05*
FFA (mmol/l)	1.03 $\pm$ 0.25	0.49 $\pm$ 0.07**	0.45 $\pm$ 0.07**
Cholesterol (mmol/l)	6.4 $\pm$ 0.5	6.2 $\pm$ 0.4	6.5 $\pm$ 0.5
Glucose (mmol/l)	9.8 $\pm$ 1.8	9.9 $\pm$ 1.1	12.2 $\pm$ 2.4
Systolic BP (mmHg)	161 $\pm$ 8	132 $\pm$ 4*	136 $\pm$ 5**
Diastolic BP (mmHg)	109 $\pm$ 6	86 $\pm$ 3***	89 $\pm$ 2***
Pulse rate (beats/min)	84 $\pm$ 4	64 $\pm$ 3***	81 $\pm$ 4

Student's paired sample *t*-test: * $P < 0.01$

** $P < 0.05$

*** $P < 0.002$

Conversion: SI to traditional units: HDL; 1 mmol/l = 39 mg/100 ml.

Triglycerides: 1 mmol = 89 mg/100 ml.

FFA: 1 mmol = 1 mEq/l.

Cholesterol: 1 mmol/l = 39 mg/100 ml.

Glucose: 1 mmol = 18 mg/100 ml.

well *et al.*, 1961; Furman *et al.*, 1961; Lewis *et al.*, 1972), thus it would be prudent to avoid treatment that might accentuate such apparently deleterious changes.

It has been demonstrated that treatment of hypertension with many β -adrenoceptor blockers, particularly propranolol, has resulted in a fall in HDL and a rise in triglyceride levels (Tanaka *et al.*, 1976; Waal-Manning & Simpson, 1977; Shaw *et al.*, 1978; Day *et al.*, 1979; Leren *et al.*, 1980). Inconsistent alterations in FFA levels have also been demonstrated (Tanaka *et al.*, 1976; Day *et al.*, 1979).

Our study of hypertensive, insulin-dependent diabetics suggests that oxprenolol produces no significant alteration in either the HDL or triglyceride fractions in such patients. This is of some practical interest as out patients, in accordance with earlier reports (Cornwell *et al.*, 1961; Furman *et al.*, 1961), exhibited HDL values at, or below, the lower limits of normal. Also an inverse relationship between HDL and very low density lipoprotein triglyceride, the prominent form of triglyceride in the fasting state, has been documented by Miller & Miller (1975). Furthermore, when both HDL and triglycerides have been measured during administration of β -adrenoceptor blockers, the levels of each have moved consistently in opposite directions—HDL has gone down, whereas, triglycerides have risen (Tanaka *et al.*, 1976; Helgeland *et al.*, 1978 a, b; Leren *et al.*, 1980). Given these earlier findings concerning the effects of β -adrenoceptor blockers, the absence of any such alterations by oxprenolol is difficult to explain. Day *et al.* (1979) suggested differing magnitudes of effect in each β -adrenoceptor blocker, so that oxprenolol might just be minimal, although another explanation may be the intrinsic sympathomimetic activity present in this preparation. A further mode of action, other than the well known anti-lipolytic effect (Tanaka *et al.*, 1976), might explain the apparent paradox of lowered FFA in the absence of any rise in triglycerides.

During the taking of methyldopa, fasting triglycerides were significantly elevated ($P < 0.01$) in all our patients, a finding previously undocumented, and this was coupled with a fall in FFA levels, a result suggesting an anti-lipolytic effect possibly due to a reduced sympathetic output from the central nervous system. The change in triglyceride levels was of greater magnitude than that found in long term trials such as the Oslo study (Helgeland *et al.*, 1978 a, b), which revealed some rise in triglyceride levels when methyldopa had been added to hydrochlorthiazide. However, in our study, the order of treatment was randomised, and samples were taken under uniform fasting conditions; therefore, the rise obtained may more closely reflect the effect of methyldopa. It is of interest to note that there was no accompanying fall in HDL when the triglycerides rose.

Although drug induced alterations in HDL, triglycerides, and FFA have been well documented during the last fifteen years, the clinical relevance will not become apparent until the completion of long term studies using these particular anti-hypertensive agents; although no beneficial effect has, so far, been demonstrated on the incidence of myocardial infarction in patients treated for hypertension. It seems reasonable to avoid preparations that alter particular lipoproteins in a direction that is known to be associated with an increased risk of CHD, such as HDL, and perhaps triglycerides, particularly in diabetics with their abnormal lipid metabolism and increased incidence of cardiovascular complications.

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