Br. J. clin. Pharmac. (1982), **13**, 441S–444S

ANTIHYPERTENSIVE DRUGS AND BLOOD LIPIDS: THE OSLO STUDY

P. LEREN, I. EIDE, O.P. FOSS, A. HELGELAND, I. HJERMANN, I. HOLME, S.E. KJELDSEN & P.G. LUND-LARSEN

Medical Out-Patient Clinic, Medical Department (7), Central Laboratory, and Life Insurance Companies' Institute for Medical Statistics, Ullevaal Hospital, Oslo, Norway

1 This report presents the effects on blood lipids and uric acid of six different antihypertensive drugs, used alone and of five different combinations of two antihypertensive drugs.

2 Prazosin significantly lowered serum LDL + VLDL cholesterol and total triglycerides. Atenolol lowered LDL + VLDL cholesterol to a smaller but significant extent. Both pindolol and hydrochlorothiazide (HCTH) were without effect, while oxprenolol significantly increased total triglycerides. Propranolol significantly lowered HDL cholesterol and increased total triglycerides and uric acid.

3 The combination prazosin and pindolol had a favourable effect on the lipid profile, while the combination propranolol and HCTH lowered HDL cholesterol but increased total triglycerides. Propranolol and prazosin lowered HDL cholesterol, while methyldopa and HCTH, and HCTH and amiloride were without effect on blood lipids.

4 It is suggested that the metabolic effects of antihypertensive drugs could be of special importance in long-term treatment of mild hypertension.

Introduction

It is a challenge to the medical profession, that, while antihypertensive treatment has proved to be effective in preventing so-called pressure-related hypertensive complications, such as stroke and renal failure, antihypertensive drugs have not unequivocally shown a preventive effect on the incidence of coronary heart disease (CHD). This fact may have many causes, e.g. the time factor, and other co-operative risk variables for the development of CHD. One possible contributing factor may also be the unfavourable, metabolic effects of some antihypertensive drugs. Recently, the effect on lipid metabolism of hypertension therapy has been highlighted (Lancet, 1980).

The discovery that the high-density-lipoprotein (HDL) is a CHD anti-risk factor has modified the lipid theory of atherogenesis. At the present time it can be stated that high coronary risk is associated with high levels of cholesterol-rich low-density-lipoprotein (LDL) and its triglyceride-rich precursor, the very-low-density lipoprotein (VLDL), and with a low level of HDL-cholesterol.

In the Oslo study, which is a combined epidemiological-preventive investigation of CHD in young and middle-aged men, we have undertaken some long-term projects involving large numbers of patients. Among these is a 5 year controlled drug trial of mild hypertension (WHO 1). After 3 years (in this paper called the 3 year study), blood lipids were studied in carefully matched subgroups (Helgeland *et al.*, 1978a). In addition we have also undertaken some short term metabolic studies of small samples of healthy men with mild hypertension. This paper reports the effects on blood lipids and uric acid of the β-adrenoceptor blocking drugs, propranolol, pindolol, oxprenolol and atenolol, the α-adrenoceptor antagonist prazosin and the diuretic hydrochlorothiazide used alone or in the following combinations: propranolol + prazosin, pindolol + prazosin, propranolol + hydrochlorothiazide, methyldopa + hydrochlorothiazide and hydrochlorothiazide + amiloride.

Methods

The participation of the Oslo Study in the WHO co-operative lipid reference programme has shown that cholesterol and triglyceride values deviated only insignificantly from reference values. Details about laboratory methods and study designs have previously been published (Helgeland *et al.*, 1978b; Kjeldsen

0306–5251/82/130 441–04 $01.00

et al., 1982; Leren et al., 1980, 1981). In all but one study (Helgeland et al., 1978b) drug treatment was randomized. In two of the studies (Kjeldsen et al., submitted for publication; Leren et al., 1981) a cross-over design with wash-out periods of 5–8 weeks was used, whereas parallel groups were used in one study (Leren et al., 1981), and also in the unpublished continuation of this study analysing the effect of the addition of prazosin and amiloride to pindolol and hydrochlorothiazide, respectively.

The term, cholesterol ratio, is the ratio between HDL cholesterol × 100 and total cholesterol minus HDL cholesterol. This ratio has also been called 'anti-atherogenic index'.

Drug treatment

In all studies, except the 3-year study, a prefixed and unchanged dose of the antihypertensive drugs was used. The drugs were administered for varying lengths of time (see Tables 1 and 2).

Monotherapy only In the propranolol–prazosin study (Leren et al., 1980) the doses were 80 mg twice daily and 2 mg twice daily, respectively. In the pindolol–hydrochlorothiazide study (Leren et al., 1981) the doses were 15 mg and 50 mg, respectively, both once daily. Finally, in the oxprenolol–atenolol study (Kjeldsen et al., submitted for publication) the doses were 80 mg and 50 mg, respectively, both twice daily.

Two drugs concomitantly Propranolol + prazosin were given in doses of 80 mg twice daily plus 2 mg twice daily, pindolol + prazosin, 15 mg once daily plus 2mg twice daily, and hydrochlorothiazide + amiloride (Moduretic), 50 mg + 5 mg, respectively, both once daily. Finally, in the 3-year study of methyldopa + hydrochlorothiazide the doses were 250 mg–500 mg twice daily + 50 mg once daily, and propranolol + hydrochlorothiazide, 40–160 mg twice daily + 50 mg once daily.

Results

In Table 1 the results of three different studies (Kjeldsen et al., submitted for publication; Leren et al., 1980, 1981) have been summarized. The short-term effect of six different antihypertensive drugs is compared with pretreatment values. There is a striking difference between prazosin and propranolol, the former showing a direct favourable effect on blood lipids, while the latter seems to have a disadvantageous effect both on blood lipids and uric acid. Pindolol is without effect while atenolol shows a smaller but significant beneficial effect on LDL + VLDL cholesterol. The atenolol-induced increase of triglycerides is large, but owing to inter-individual variation, the increase does not reach the 5% level of significance. Oxprenolol is also without effect, except for a 22% triglyceride increase. Finally, hydrochlorothiazide (HCTH) did not significantly influence either blood lipids or uric acid.

Table 2 shows the effect on lipids and uric acid of five different drug combinations, as compared with pretreatment values. In the 3-year study, pretreatment HDL cholesterol was analysed only in stored deep-frozen specimens, and the results have only been used for the matching of the study groups. Therefore, the drug effect on HDL cholesterol has been calculated as the difference from the mean of two comparable treatment groups (results from 3-year hydrochlorothiazide-alone group not given), and the untreated control group.

Table 1 Metabolic effects (% change) of some antihypertensive drugs after administration to men aged 47–55 years with hypertension WHO I

Drug	Prazosin	Propranolol	Hydrochlorothiazide	Pindolol	Atenolol	Oxprenolol
Number of patients	$n = 23$	$n = 23$	$n = 10$	$n = 10$	$n = 20$	$n = 20$
Duration of treatment	8 weeks	8 weeks	10 weeks	10 weeks	5 weeks	5 weeks
Study	Leren *et al.* (1980)		Leren *et al.* (1981)		Kjeldsen *et al.* (submitted for publication)	
Total cholesterol	−8.9***	NS	NS	NS	−4.9*	NS
LDL + VLDL cholesterol	−10.1***	NS	NS	NS	−5.9*	NS
HDL cholesterol	NS	−13.0***	NS	NS	NS	NS
Cholesterol ratio[1]	+7.0*	−15.2***	NS	NS	NS	NS
Total triglycerides	−16.2***	+24.0***	NS	NS	NS	+22.0*
Uric acid	NS	+10.4**	NS	NS	NS	NS

***$P<0.001$, **$P<0.01$, *$P<0.05$.
NS = not significant
[1] $\frac{\text{HDL cholesterol} \times 100}{\text{Total cholesterol} - \text{HDL cholesterol}}$

Table 2 Metabolic effects (% change) of some antihypertensive drug combinations after administration to men aged 40–45 years with hypertension WHO I.

Drug combination	Prazosin + pindolol	Prazosin + propranolol	HCTH + amiloride	Methyldopa + HCTH	Propranolol + HCTH	Untreated controls
Number of patients	$n=10$	$n=22$	$n=10$	$n=33$	$n=33$	$n=33$
Duration of treatment	14 weeks	8 weeks	14 weeks	3 years	3 years	3 years
Total cholesterol	NS	NS	NS	NS	NS	NS
LDL + VLDL cholesterol	−12.0*	NS	NS			
HDL cholesterol	NS	−7.5**	NS	NS†	−18.1**†	NS†
Cholesterol ratio	NS	NS	NS			
Total triglycerides	NS	NS	NS	NS	+44.3**	NS
Uric acid	+7.3*	+13.6**	+1.39*	NS	+21.8*	NS

**$P<0.01$, *$P<0.05$
NS = not significant
†Difference from mean of two treatment and a control group
HCTH = hydrochlorothiazide

Again, a difference in effect on lipids between the β-adrenergic receptor blockers, propranolol and pindolol, can be seen. With the propranolol–prazosin combination the unfavourable propranolol, and the favourable prazosin effects have mainly disappeared, only a slight reduction of HDL persists, while with the pindolol–prazosin combination, the favourable prazosin effect on LDL + VLDL cholesterol is still present, probably due to the fact that pindolol has no effect on blood lipids. The addition of amiloride to hydrochlorothiazide did not alter the lack of effect of the thiazide on blood lipids; however, a moderate uric acid increase was seen.

In the 3-year study the drug combination of methyldopa and hydrochlorothiazide did not change blood lipids and uric acid, in contrast to the propranolol–thiazide combination that markedly lowered HDL cholesterol and increased total triglycerides and uric acid.

Discussion

This report presents the effect on blood lipids of six different antihypertensive drugs used alone and of five different combinations of two antihypertensive drugs.

Most of the studies are of short duration and involve few patients, which calls for some caution when drawing conclusions. On the other hand, the studies were undertaken with homogenous groups of persons, all in a steady metabolic state. All were healthy men, with a symptomfree WHO I mild hypertension. In contrast to some long-term observational studies, no drugs other than the test drugs were taken during the trial, and the co-operation of the men as out-patients was excellent, probably due to the fact that they were selected from a large cohort as being especially co-operative. Thus, no control examinations or laboratory data were lost during the study periods. Lastly, all studies, with only one exception (Helgeland *et al.*, 1978b), were specially designed to evaluate the lipid effect of the test drugs.

Both short-term and long-term studies have shown an unfavourable effect of propranolol on blood lipids including a decrease of HDL cholesterol and an increase in triglycerides (Day *et al.*, 1979; Helgeland *et al.*, 1978b; Leren *et al.*, 1980; Tanaka, 1976; Waal-Manning, 1976), while one long-term observational study comparing 51 male and female patients, aged 41–71 years, receiving β-adrenoceptor blocking drugs (mainly propranolol) plus a thiazide (80% of the patients), with 42 patients on methyldopa, clonidine, prazosin, or a thiazide in varying doses, but not on a β-adrenoceptor blocker, failed to show any significant difference in lipid and uric acid levels between the groups (Kristensen, 1981).

In this report neither pindolol, oxprenolol nor atenolol induced a fall in HDL cholesterol, while England *et al.* (1980) reported a reduction in HDL cholesterol both with atenolol and metoprolol in combination with a thiazide. Thus, both β_1-selective and non-selective adrenergic receptor blockers have been shown to possess this negative effect on HDL cholesterol. However, pindolol and oxprenolol are different from other β-adrenoceptor blockers in possessing intrinsic sympathomimetic activity (ISA), which is especially marked with pindolol. It seems logical to attribute the lack of effect of pindolol and oxprenolol on HDL cholesterol to their ISA-effect. Another study of oxprenolol also showed no effect on HDL cholesterol (Hoffbrand *et al.*, 1980). However, in the studies presented in this report, atenolol, which is devoid of ISA, did not have any significant effect on HDL cholesterol. This observation throws some doubt on the ISA-theory for the difference in lipid

effects of β-adrenoceptor blocking drugs. Our atenolol results, however, are in conflict with those of England *et al.* (1980), and the effect of this β-adrenergic receptor blocker on blood lipids should be investigated in further studies before abandoning the ISA-theory for the lack of HDL decreasing effect of pindolol and oxprenolol.

Previous studies have reported an increase in serum triglycerides and uric acid during treatment with thiazides (Ames & Hill, 1976; Joos *et al.*, 1980). Helgeland *et al.* (1978a) have shown that those who reacted with a triglyceride increase were those who gained weight during thiazide treatment, while those on hydrochlorothiazide who avoided weight gain showed no rise in serum triglycerides or uric acid. In the present short-term thiazide study, and in our previously reported 3-year study of 26 men, aged 40–49 years (Helgeland *et al.*, 1978a), body weight remained unchanged and no serum triglyceride increase was observed.

The addition of amiloride to hydrochlorothiazide (Moduretic) did not change its lipid profile.

With regard to the effect on blood lipids, the α-adrenoceptor blocker, prazosin, seems to be the antihypertensive drug of choice. The prazosin treated patients showed a significant reduction of the atherogenic cholesterol fractions in the LDL + VLDL lipoproteins, and also a reduction in triglyceride levels without interfering with serum HDL cholesterol. The cholesterol reduction with prazosin was of the same order as that obtained with 1.6 g clofibrate in a large international primary-prevention study (Oliver *et al.*, 1978). When combined with propranolol, prazosin to some extent eliminated the disadvantageous lipid effects of this β-adrenoceptor blocker, and in combination with pindolol, a LDL + VLDL lipoprotein fractions were reduced by 12%. Thus, the combination of prazosin and pindolol has the most favourable lipid profile of the antihypertensive drug combinations studied so far. However, these effects should be confirmed in long-term studies.

In the 3-year study the combined treatment with propranolol and hydrochlorothiazide induced unfavourable changes in the lipid and uric acid levels, while the combination of methyldopa and hydrochlorothiazide showed no unfavourable metabolic effects.

The clinical importance of the observed effects on blood lipids and uric acid of some antihypertensive drugs is uncertain, and caution must be exercised when the practical implications are decided. However, the metabolic effects of antihypertensive drugs should be taken into consideration when deciding long-term treatment of mild hypertension, especially for young people.

References

AMES, R.P. & HILL, P. (1976). Elevation of serum lipid levels during diuretic therapy of hypertension. *Am. J. Med.*, **6**, 748–757.

DAY, I.L., SIMPSON, N., METCALFE, J. & PAGE, R.I. (1979). Metabolic consequences of atenolol and propranolol in treatment of essential hypertension. *Br. med. J.*, **1**, 77–80.

ENGLAND, I.D.F., SIMONS, L.A., GIBSON, J.C. & CARLTON, M. (1980). The effect of metoprolol and atenolol on plasma high-density-lipoprotein levels in man. *Clin. exp. Pharmac. Physiol.*, **7**, 329–333.

HELGELAND, A., HJERMANN, I., LEREN, P., ENGER, S.C. & HOLME, I. (1978b). High-density lipoprotein cholesterol and antihypertensive drugs. The Oslo Study. *Br. med. J.*, **2**, 403.

HELGELAND, A., HJERMANN, I., HOLME, I. & LEREN, P. (1978a). Serum triglycerides and serum uric acid in untreated and thiazide-treated patients with mild hypertension. The Oslo Study. *Am. J. med.*, **64**, 34–38.

HOFFBRAND, B.I., CHRISP, A.J., CARRUTHERS, M., EBBALT, A.F. & KENNEDY, P.E.G. (1980). Abstracts, *8th European Congress of Cardiology*, Paris.

JOOS, C., KEWITZ, H. & REINHOLD-KOURNIATI, D. (1980). Effects of diuretics on plasma lipoproteins in healthy men. *Eur. J. clin. Pharmac.*, **17**, 251–257.

KRISTENSEN, B.Ø. (1981). Effect of long-term treatment with betablocking drugs on plasma lipids and lipoproteins. *Br. med. J.*, **2**, 191–192.

LANCET (1980). Editorial. *Lancet*, **ii**, 19–20.

LEREN, P., FOSS, O.P., HELGELAND, A., HJERMANN, I., HOLME, I. & LUND-LARSEN, P.G. (1980). Effect of propranolol and prazosin on blood lipids. The Oslo Study. *Lancet*, **ii**, 4–6.

LEREN, P., FOSS, O.P., HELGELAND, A., HJERMANN, I. & HOLME, I. (1981). Effect of pindolol and hydrochlorothiazide on blood lipids. The Oslo Study. *Clinical Trial J.*, **18**, 254–261.

OLIVER, M.F., HEADY, J.A. & COOPER, J. (1978). A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. *Br. Heart J.*, **40**, 1069–1118.

TANAKA, N. (1976). Effect of chronic administration of propranolol on lipoprotein composition. *Metabolism*, **25**, 1071–1075.

WAAL-MANNING, H.J. (1976). Can β-blockers be used in diabetic patients? *Drugs*, **11** suppl. 1, 121.