Double-blind comparison of the effects of long-term treatment with doxazosin or atenolol on serum lipoproteins

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1 The effects on plasma lipids and apoproteins A-I and B of oral administration of doxazosin and atenolol over a 20-week period were studied in 42 patients with mild to moderate essential hypertension.

2 Total plasma cholesterol decreased by 8.9% ($P < 0.01$) and LDL cholesterol by 16.9% ($P < 0.01$) after 20 weeks' treatment with doxazosin.

3 Total HDL cholesterol and HDL₂ cholesterol concentrations increased slightly during doxazosin treatment and the increase in HDL₂ level at 4 weeks was statistically significant ($P < 0.05$). At 20 weeks, the levels of total HDL cholesterol and HDL₂ were significantly ($P < 0.05$) lower with atenolol than with doxazosin.

4 The ratio HDL/total cholesterol increased during doxazosin treatment ($P < 0.05$ at 4, 12 and 20 weeks). The HDL/total cholesterol ratio was significantly higher after 20 weeks with doxazosin than with atenolol ($P < 0.05$).

5 The levels of VLDL cholesterol and triglycerides increased significantly ($P < 0.01$) during atenolol treatment.

6 The concentrations of apoproteins A-I and B did not change significantly during treatment with doxazosin or with atenolol but at 20 weeks the ratio of apo A-I to apo B was significantly ($P < 0.05$) lower with atenolol than with doxazosin.

7 On the basis of these results, doxazosin would seem to have significant favourable effects on the serum lipid profile.

Keywords apoproteins atenolol doxazosin hypertension serum lipids

Introduction

The fact that treatment of hypertension has shown no definite preventive effect on the incidence of coronary heart disease has aroused interest in lipid metabolism in hypertension (Editorial, *Lancet*, 1980). As previously reported (Ames & Hill, 1976; Helgeland *et al.*, 1978; Day *et al.*, 1979), some of the drugs most commonly used in the treatment of hypertension may have adverse effects on serum lipids. Atenolol, for example, has been reported to increase the plasma triglyceride concentration, whereas plasma cholesterol levels have remained almost unchanged (Day *et al.*, 1979; Lehtonen & Marniemi, 1984). The level of HDL cholesterol during atenolol treatment was found to be significantly lower than before treatment and this decrease was due to the decrease in HDL₂

cholesterol concentration (Lehtonen & Marniemi, 1984).

On the other hand, reductions in serum triglyceride and cholesterol concentrations have been observed in hypertensive subjects during treatment with prazosin (Leren *et al.*, 1980). Doxazosin, a new quinazoline antihypertensive of the post-synaptic α_1 -adrenoceptor blocking series, is related to prazosin.

The purpose of this study was to compare the effects of doxazosin and atenolol on serum lipids and lipoproteins in patients receiving these drugs for the treatment of hypertension.

Methods

Forty-two patients (21 females, 21 males, aged 33–67 years) with mild to moderate essential

hypertension (90–114 mmHg) were included in the study. Many of the patients were receiving some antihypertensive treatment. Informed consent was obtained from all patients. Basal laboratory measurements were made, and the treatment was discontinued before the initiation of the placebo treatment. After 4 weeks treatment with placebo the patients were randomly allocated to treatment with either doxazosin 1 mg once daily or atenolol 50 mg once daily. The dose of doxazosin was increased, if necessary, to 2 mg once daily after 2 weeks treatment and further increased stepwise up to 16 mg once daily after later treatment periods to achieve a standing diastolic pressure below 90 mmHg. Correspondingly, the dose of atenolol was increased up to 100 mg once daily. Blood pressures were measured and fasting blood samples were drawn at 4, 12 and 20 weeks of treatment. No dietary advice was given to the patients.

Total cholesterol and triglyceride concentration were determined enzymatically (Röschlau *et al.*, 1974; Wahlefeld, 1974). HDL cholesterol was determined after precipitation of very low density

lipoproteins (VLDL) and low density lipoproteins (LDL) with heparin and manganese chloride (Warnick & Albers, 1978), followed by differential precipitation with low molecular weight dextran sulphate for separation of the HDL subfractions, HDL₂ and HDL₃ (Gidez *et al.*, 1982). LDL cholesterol was determined according to Beaumont *et al.* (1970).

The concentrations of serum apolipoproteins A-I and B were estimated by the measurement of immunoprecipitation at 340 nm by specific antisera, using the analysis kit produced by Orion Diagnostica, Helsinki, Finland.

Differences in the concentrations during doxazosin and atenolol treatments were assessed by the paired Student's *t*-test (Taylor, 1972).

Results

Compared with pretreatment values total plasma cholesterol was significantly lower after 12 ($P < 0.05$) and 20 ($P < 0.01$) weeks of treatment with

Table 1 Plasma lipids (mmol⁻¹) during therapy with doxazosin or atenolol

	Baseline value	Placebo		Active treatment	
		4 weeks	4 weeks	12 weeks	20 weeks
Cholesterol					
Doxazosin	6.61±1.07(22)	6.62±1.01(21)	6.32±1.05(21)	6.08±1.41(19) ^{a,b}	6.02±1.22(18) ^{a,**b}
Atenolol	6.25±1.14(20)	6.00±1.27(20) ^b	6.48±1.12(17) ^a	6.22±1.20(18)	6.43±1.42(16)
LDL cholesterol					
Doxazosin	4.85±1.13(21)	4.83±1.06(21)	4.49±1.07(21)	4.16±1.35(19) ^{a,b}	4.03±1.13(18) ^{a,**b}
Atenolol	4.39±1.20(20)	4.27±1.31(20)	4.56±1.18(17)	4.27±1.12(18)	4.51±1.38(16)
VLDL cholesterol					
Doxazosin	0.61±0.30(21)	0.59±0.24(21)	0.54±0.22(21)	0.58±0.23(19)	0.59±0.22(18)
Atenolol	0.74±0.35(20)	0.53±0.26(20)	0.70±0.31(17) ^a	0.76±0.29(18) ^a	0.74±0.28(16) ^{**a}
HDL cholesterol					
Doxazosin	1.62±0.44(21)	1.56±0.41(19)	1.66±0.37(19)	1.69±0.37(17)	1.75±0.44(17) ^c
Atenolol	1.62±0.50(18)	1.51±0.38(17)	1.51±0.40(17)	1.41±0.46(17)	1.44±0.41(16) ^{**b}
HDL₂					
Doxazosin	0.67±0.34(21)	0.70±0.35(19)	0.80±0.32(19) ^{a,b}	0.77±0.29(17)	0.80±0.28(17) ^c
Atenolol	0.74±0.36(18)	0.68±0.23(17)	0.54±0.45(17)	0.60±0.24(17)	0.60±0.19(16)
HDL₃					
Doxazosin	0.95±0.28(21)	0.87±0.24(19) ^b	0.86±0.19(19)	0.91±0.23(17)	0.95±0.23(17)
Atenolol	0.88±0.22(18)	0.83±0.19(17)	0.97±0.36(17)	0.81±0.21(17)	0.85±0.26(16)
Triglycerides					
Doxazosin	1.49±0.72(22)	1.41±0.58(21)	1.31±0.52(21)	1.39±0.87(19)	1.42±0.75(18)
Atenolol	1.78±0.83(20)	1.30±0.63(20)	1.69±0.75(17) ^a	1.82±0.71(17) ^a	1.78±0.67(18) ^{**a}

n is given in parentheses

^a $P < 0.05$, ^{**} $P < 0.01$

^aplacebo vs active treatment values

^bbaseline vs treatment values

^cdoxazosin vs atenolol

Table 2 Plasma apolipoprotein concentrations (g l^{-1}) and the ratios of apo A-I to apo B and HDL cholesterol to total cholesterol during therapy with doxazosin and atenolol

	<i>Baseline value</i>	<i>Placebo</i>	<i>Active treatment</i>		
		<i>4 weeks</i>	<i>4 weeks</i>	<i>12 weeks</i>	<i>20 weeks</i>
Apoprotein A – I					
Doxazosin	1.61±0.34(22)	1.68±0.31(21)	1.68±0.36(20)	1.65±0.33(18)	1.65±0.41(19)
Atenolol	1.64±0.34(20)	1.68±0.35(20)	1.73±0.45(16)	1.59±0.39(18)	1.57±0.29(15)
Apoprotein B					
Doxazosin	1.09±0.32(22)	1.12±0.24(21)	1.07±0.24(20)	1.03±0.23(18)	1.01±0.20(19)
Atenolol	1.15±0.27(20)	1.07±0.25(20)	1.18±0.26(16)	1.13±0.26(18)	1.14±0.29(15)
Apo A – I/Apo B					
Doxazosin	1.62±0.65(22)	1.60±0.55(20)	1.64±0.49(20)	1.63±0.34(18)	1.74±0.50(18)* ^c
Atenolol	1.50±0.45(20)	1.65±0.54(20)	1.53±0.44(16)	1.46±0.50(18)	1.44±0.46(15)
HDL/total cholesterol					
Doxazosin	0.19±0.60(22)	0.19±0.05(21)	0.21±0.06(21)* ^a	0.23±0.06(19)* ^{a,b}	0.24±0.06(18)* ^{a,b,c}
Atenolol	0.19±0.07(20)	0.21±0.07(20)* ^b	0.19±0.06(17)	0.20±0.06(18)	0.19±0.06(16)

n is given in parentheses

* $P < 0.05$, ** $P < 0.01$

^aplacebo vs active treatment values

^bbaseline vs treatment values

^cdoxazosin vs atenolol

doxazosin; the 20 week decrease in cholesterol concentration was 8.9% (Table 1). This decrease was due to a reduction in LDL cholesterol by 0.80 mmol l^{-1} (16.9%, $P < 0.01$) over 20 weeks. Total HDL cholesterol and HDL₂ concentrations increased slightly during doxazosin treatment, but the only significant increase ($P < 0.05$) was in HDL₂ at 4 weeks with doxazosin. HDL₃ levels initially decreased slightly ($P < 0.05$) at 4 weeks with placebo.

During atenolol treatment, total HDL cholesterol decreased from 1.51 ± 0.38 to $1.44 \pm 0.41 \text{ mmol l}^{-1}$. At 20 weeks the total HDL cholesterol and HDL₂ were significantly lower ($P < 0.05$) with atenolol than with doxazosin. Total plasma cholesterol and LDL cholesterol concentrations tended to be slightly higher after 20 weeks' treatment with atenolol compared with pretreatment values, and VLDL cholesterol concentration significantly increased ($P < 0.01$) during atenolol treatment.

There were no significant changes in the concentrations of serum triglycerides during treatment with doxazosin but the level of serum triglycerides increased significantly during atenolol treatment. The ratio of HDL to total cholesterol increased during doxazosin treatment ($P < 0.05$ at 12 and 20 weeks) (Table 2). After 20 weeks the HDL/total cholesterol ratio was significantly higher with doxazosin than with atenolol ($P < 0.05$).

The concentrations of apoproteins A-I and B did

not change significantly during treatment with doxazosin or with atenolol but the ratio apo A-I/apo B was significantly lower ($P < 0.05$) with atenolol than with doxazosin after 20 weeks.

The patient population in this study represents a subpopulation of a larger study fully reported by Frick *et al.* (1986). Blood pressure changes in this subpopulation were consistent with those in the full study population.

Discussion

The effects of β -adrenoceptor antagonists and diuretics on plasma lipids have become a matter of concern. Many β -adrenoceptor blockers have been studied in this respect and the general finding is that serum triglycerides increase, to varying degrees, in patients treated with propranolol (Shaw *et al.*, 1978), atenolol (Day *et al.*, 1979) or metoprolol (Shaw *et al.*, 1978). An increase in the concentration of serum total cholesterol and LDL cholesterol has been found during treatment with sotalol (Lehtonen & Viikari, 1979). The level of HDL cholesterol seems to decrease during treatment with propranolol (Leren *et al.*, 1980), sotalol (Lehtonen & Viikari, 1979), atenolol and metoprolol (England *et al.*, 1980). Pindolol, with marked intrinsic sympathomimetic activity, significantly increases plasma HDL/total cholesterol ratio (Lehtonen *et al.*, 1982).

In the present investigation the level of HDL cholesterol decreased slightly during atenolol treatment. These results agree with earlier studies (Lehtonen & Marniemi, 1984; England *et al.*, 1980), but the smaller changes may be due to the smaller dose of atenolol (50 mg daily) used in some patients, since in an earlier study (Rössner & Weiner, 1984) little change in serum lipids occurred during treatment with atenolol 50 mg daily. The decrease in HDL cholesterol seems to be due to the decrease in the HDL₂ level. In the present study, the concentrations of serum total cholesterol and triglycerides increased significantly during atenolol treatment.

Patients treated with the α_1 -adrenoceptor selective postsynaptic blocker, prazosin, have shown a significant reduction in the atherogenic cholesterol fractions in LDL + VLDL and also a reduction in triglyceride levels, without interfering with serum HDL cholesterol (Leren *et al.*, 1980).

Doxazosin is a new selective α_1 -adrenoceptor antagonist and is related to prazosin. The current study shows that a decrease occurred in serum cholesterol and LDL cholesterol levels during 20 weeks' treatment with doxazosin. The concentrations of total HDL cholesterol, HDL₂ cholesterol and the ratio of HDL/total cholesterol were higher after 20 weeks' treatment with doxazosin than before or after 20 weeks' treatment with atenolol.

In the current study, relatively few changes occurred in the levels of apoprotein A-I or apo B during treatment with doxazosin or atenolol, but the ratio apo A-I/apo B decreased (not significant) after 20 weeks with atenolol.

Earlier reports have shown decreased apo A-I levels and increased apo B levels in patients with coronary heart disease (de Backer *et al.*, 1982). The data from the Framingham study have demonstrated that the higher the concentrations of HDL, the lower the risk of coronary artery disease, and that HDL is an independent factor in the prediction of risk (Gordon *et al.*, 1977).

With regard to the effect on plasma lipids, doxazosin seems to have a favourable effect on the lipid profile compared with the effect of atenolol.

In the selection of therapy for hypertension it is currently held that the satisfactory lowering of blood pressure must be the primary aim, owing to the beneficial effect on pressure-mediated complications, and the effects of drugs on plasma lipoproteins must remain secondary considerations because their role in the pathogenesis of coronary heart disease is unproven. However, drugs with maximal beneficial effects on reducing the risk

factors for coronary heart disease should be preferred.

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