Br. J. clin. Pharmac. (1982), **13**, 431S–434S

HDL CHOLESTEROL AND β-ADRENOCEPTOR BLOCKING AGENTS IN A 5 YEAR MULTIFACTORIAL PRIMARY PREVENTION TRIAL

T.A. MIETTINEN, H. VANHANEN, J.K. HUTTUNEN, V. NAUKKARINEN, S. MATTILA, T. STRANDBERG & T. KUMLIN

Second Department of Medicine, University of Helsinki, and Public Health Laboratory of Finland, Helsinki, Finland

1 Serum HDL cholesterol measured at the end of a 5 year multifactorial primary prevention trial, aimed to reduce risk factor levels and incidence of ischaemic heart disease, revealed quite low values in drug-treated subjects.

2 Analysis of subgroups treated with β-adrenoceptor blocking agents (mainly pindolol) alone or in different combinations with diuretics showed inconsistent effects of β-adrenoceptors blockers on serum HDL cholesterol. HDL cholesterol levels in patients treated with pindolol with or without a diuretic were not different from those of the risk-free control group.

3 Subjects on combined β-adrenoceptor blocker-hypolipidaemic treatments had lower HDL-cholesterol than those on hypolipidaemic agents alone.

4 Withdrawal of pindolol at the end of the trial caused a small but significant increase in serum HDL cholesterol in a small subgroup of mildly hypertensive patients. Thus, pindolol appears to have slightly reduced serum HDL cholesterol but the relevance of this small decrease on the incidence of ischaemic heart disease is questionable.

Introduction

β-adrenoceptor blocking agents are frequently used in the treatment of hypertension. Recent studies (Waal-Manning, 1976; Tanaka *et al.*, 1976; Helgeland *et al.*, 1978; Streja & Mymin, 1978; Lehtonen & Viikari, 1979; Leren *et al.*, 1980) have revealed that these agents frequently increase plasma triglycerides and decrease HDL cholesterol, two plasma constituents which usually exhibit a negative correlation with each other. The significance of an increased triglyceride level as a risk factor of coronary heart disease is still a controversial question while epidemiological studies indicate that low HDL cholesterol is a strong negative risk factor (Miller *et al.*, 1977; Kannel *et al.*, 1979). It is thus logical to infer that the unfavourable effect of β-adrenoceptor blockers on HDL may counteract the beneficial effect of lowering blood pressure in ischaemic heart disease especially during long-term treatment. In the present study serum HDL cholesterol was measured at the end of a 5 year multifactorial primary prevention trial in different treatment groups in subjects on β-adrenoceptor blockers alone or in combination with diuretics and/or hydralazine or hypolipidaemic drugs.

Methods

All subjects studied were active participants of a 5 year multifactorial trial aimed at primary prevention of ischaemic heart disease. The trial was started in 1974 when 1222 men with one or more of the following risk factors were randomly allocated to intervention ($n = 612$) and control ($n = 610$) groups: blood-pressure $> 160/95$ mmHg, serum cholesterol > 7.1 mmol/l, serum triglycerides > 1.7 mmol/l, blood glucose 1 h after oral glucose load (1 g/kg body weight) > 9.0 mmol/l, relative body weight $> 120\%$, smoking > 10 cigarettes/day.

The intervention group visited us once every 3–5 months. At each visit the participants were advised to reduce their body weight, consume a diet low in animal fat and simple carbohydrates, stop smoking and increase their physical activity. If the participants were hypertensive or hyperlipidaemic on two consecutive visits drug treatment was initiated. Hypertension was treated with β-adrenoceptor blockers (mainly pindolol or propranolol) alone or in combination with diuretics (hydrochlorthiazide and amiloride) and/or hydralazine. Other drugs were used in occasional cases. Type II hyperlipoproteinaemia (cholesterol > 7.0 mmol/l and triglycerides < 1.7 mmol/l) was treated with probucol (1–2 g/day) and in some cases with clofibrate (1.5 g/day) alone or in combination with probucol. Type IV (cholesterol < 7.1 mmol/l and triglycerides > 1.6 mmol/l) and type IIB hyperlipoproteinaemias (cholesterol > 7.0 mmol/l and triglycerides

0306–5251/82/130 431–04 $01.00

> 1.6 mmol/l) were treated with clofibrate. In subjects with type IIB abnormality probucol was added to the drug regimen, if the response of serum cholesterol to clofibrate was not adequate.

The risk control group and a risk-free control group of 539 men received no treatment or advice.

For the purpose of the present study the intervention group was divided into subgroups according to the treatment at the end of the 5 year trial (Table 1). The concentration of HDL cholesterol was determined enzymatically after heparin-manganese precipitation (Lipid Research Clinics Program Manual of Laboratory Operations, 1974; Röschlau *et al.*, 1974). Only the values at the end of the 5 year intervention period were obtained because the determination of HDL cholesterol from the serum samples drawn at the start of the study and stored frozen for 4–5 years gave unreliably low values. Total serum cholesterol and triglycerides were measured both at the entry and end of the study. HDL cholesterol, total cholesterol and triglycerides were repeatedly measured in two mildly hypertensive subgroups on a combined pindolol-diuretic treatment 2–3 months after the completion of the intervention trial. Pindolol was withdrawn for this period of time from one of those subgroups.

Results

Results in Table 1 show that, despite significantly higher triglycerides, HDL cholesterol in the diet-treated intervention subgroup of 87 subjects is similar to that in the risk-free control group at the end of the 5 year intervention period. With the exception of initial serum cholesterol, the total lipid levels are similar in the drug-treated and diet-treated subjects of the intervention group. Since antihypertensive and hypolipidaemic agents may have contributed to the low HDL cholesterol level in the drug-treated sub-

Table 1 Serum total lipids and HDL cholesterol in different groups of patients in a 5 year intervention trial. Mean ± s.e.mean (mmol/l)

Group or treatment	*Number of subjects*[a]	*Total cholesterol*		*Triglycerides*		*Final HDL cholesterol*
		Before	*Final*	*Before*	*Final*	
Risk-free control	437	6.0 ± 0.1	6.3 ± 0.1	1.16 ± 0.06	1.19 ± 0.06	1.22 ± 0.01
Risk control	404	7.0 ± 0.2	7.2 ± 0.2	1.68 ± 0.10	1.67 ± 0.11	1.16 ± 0.02
Intervention						
Diet[b]	87	6.6 ± 0.1	6.5 ± 0.1	1.63 ± 0.06	1.44 ± 0.06	1.21 ± 0.04
Any drug	237	7.4 ± 0.1	6.7 ± 0.1	1.56 ± 0.04	1.49 ± 0.04	1.02 ± 0.02
Probucol[c]	75	7.9 ± 0.01	6.7 ± 0.1	1.44 ± 0.06	1.35 ± 0.06	0.97 ± 0.05
Probucol + β-adrenoceptor blockers	44	7.6 ± 0.1	6.7 ± 0.1	1.64 ± 0.10	1.73 ± 0.12	0.81 ± 0.04
Clofibrate[c]	42	7.9 ± 0.1	7.1 ± 0.1	2.06 ± 0.14	1.62 ± 0.12	0.98 ± 0.04
Clofibrate + β-adrenoceptor blockers	43	7.3 ± 0.2	6.9 ± 0.2	2.00 ± 0.14	1.98 ± 0.14	0.90 ± 0.05
Diuretics[c]	18	7.3 ± 0.2	6.4 ± 0.2	1.40 ± 0.10	1.38 ± 0.15	0.94 ± 0.08
Diuretics + β-adrenoceptor blockers	62	6.9 ± 0.2	6.7 ± 0.1	1.58 ± 0.09	1.69 ± 0.10	1.01 ± 0.04
β-adrenoceptor blockers alone[d]	10	6.6 ± 0.2	6.6 ± 0.3	1.23 ± 0.18	1.19 ± 0.09	1.18 ± 0.06
Pindolol alone	12	6.5 ± 0.2	6.9 ± 0.3	1.56 ± 0.17	1.73 ± 0.17	1.23 ± 0.07
Probucol alone	55	7.8 ± 0.1	6.6 ± 0.1	1.32 ± 0.05	1.26 ± 0.06	1.07 ± 0.05
Probucol + pindolol	6	7.9 ± 0.4	6.7 ± 0.2	1.33 ± 0.20	1.02 ± 0.07	0.85 ± 0.05
Clofibrate alone	26	7.7 ± 0.2	7.0 ± 0.2	2.16 ± 0.19	1.59 ± 0.18	1.17 ± 0.05
Clofibrate + pindolol	6	7.6 ± 0.6	7.1 ± 0.5	1.93 ± 0.29	1.57 ± 0.15	0.93 ± 0.07
Diuretics alone	11	7.0 ± 0.3	6.6 ± 0.2	1.41 ± 0.16	1.30 ± 0.20	1.14 ± 0.07
Diuretics + pindolol	20	6.4 ± 0.2	6.6 ± 0.2	1.32 ± 0.13	1.51 ± 0.13	1.21 ± 0.05

[a]Number of subjects with final HDL cholesterol available at the moment
[b]Health education (see **Methods**) was continuous to all participants in intervention groups
[c]Other drugs, except β-adrenoceptor blockers, may have been included. Diuretics given were hydrochlorothiazide or amiloride
[d]Other than pindolol.

group of 237 subjects they were further subgrouped according to the treatment. The 75 subjects on probucol and 42 on clofibrate (other drugs except β-adrenoceptor blockers were not excluded) had fairly low HDL cholesterol, the values being even lower when β-adrenoceptor blockers (mainly pindolol) were combined with the two hypolipidaemic drugs. However, the hypertensive subjects treated with diuretics and those treated with diuretics and β-adrenoceptor blockers had similar though quite low HDL levels. It should be noted that final triglycerides were relatively high in the three subgroups on β-adrenoceptor blockers.

To explore more closely the effect of β-adrenoceptor blockers on HDL, different subgroups treated with one or two defined drugs were separated (four lowest group pairs in Table 1). Subjects treated with pindolol or other β-adrenoceptor blockers alone had a similar HDL cholesterol level to the diet treated group. The combination of pindolol with probucol or with clofibrate was again associated with lowered HDL cholesterol levels, while the subjects on diuretics and on diuretics and pindolol had similar, relatively high HDL cholesterol levels.

The results indicate that according to the cross-sectional studies long-term β-adrenoceptor blocker treatment had no consistent effect on HDL cholesterol. The lipid measurements were repeated in two small subgroups treated with pindolol (10 mg/day) plus diuretics (Table 2). In the control group which continued the use of pindolol no consistent change was observed in the blood pressure or serum lipids. Withdrawal of pindolol in the other subgroup was followed by a slight but significant increase in the systolic blood pressure ($+9 \pm 2$ mmHg) and in the HDL cholesterol level ($+0.11 \pm 0.04$ mmol/l), and by a significant decrease in triglycerides (-0.56 ± 0.2 mmol/l). The changes in triglycerides and HDL cholesterol differed significantly between the two experimental groups. Thus, long-term pindolol treatment had slightly reduced HDL cholesterol. The changes in triglycerides and HDL cholesterol caused by the withdrawal of pindolol did not correlate significantly with each other ($r = -0.172$).

Discussion

In a previous cross-sectional study (Kristensen, 1981) no significant effect was observed during long-term antihypertensive therapy with β-adrenoceptor blockers (mainly propranolol) on HDL cholesterol levels. Similar results were obtained in the present study. The low HDL cholesterol levels found in the subjects treated with hypolipidaemic agents plus β-adrenoceptor blockers may be due to the drug combination or more likely to unmatching of the groups. Withdrawal of pindolol actually revealed that the drug had decreased HDL cholesterol, at least in combination with diuretics, but this effect was so small (0.1 mmol/l) that it could not be detected by the cross-sectional analysis technique. The unfavourable effect of pindolol on HDL cholesterol appears to be less significant than that of many other β-adrenoceptor blockers, especially propranolol (Leren *et al.*, 1980). Also in our study HDL cholesterol values appeared to be lower in patients treated with other β-adrenoceptor blocking drugs with and without diuretics, in comparison with those of the risk-free control group or those treated with pindolol, with and without a diuretics.

Beneficial effect of the treatment of mild hypertension on coronary heart disease has not been proved as yet. In fact in some investigations, as in the Oslo study (Leren *et al.*, 1980) and our intervention study the incidence tends to be increased. The exact role of

Table 2 Effects (mean ± s.e.mean) of pindolol withdrawal upon serum lipids in hypertensive subjects treated with a pindolol-diuretic (hydrochlorothiazide or amiloride) combination during the preceeding 5 year intervention period

Pindolol treatment	*Total lipids (mmol/l)*		*HDL cholesterol (mmol/l)*
	Cholesterol	*Triglycerides*	
Control, pindolol continued (12)			
Measurement 1	6.5 ± 0.2	1.56 ± 0.17	1.23 ± 0.07
Measurement 2 (how long after?)	6.8 ± 0.3	1.73 ± 0.17	1.18 ± 0.05
Experimental, pindolol withdrawn (10)			
Before withdrawal	7.4 ± 0.3	1.85 ± 0.17	1.15 ± 0.06
After withdrawal (how long after?)	7.4 ± 0.3	1.28 ± 0.12*†	1.25 ± 0.06*†

Number of subjects in parenthesis
*Significant change or †difference of changes ($P < 0.05$ or less) between the two experiments.

HDL cholesterol lowering remains to be resolved. The poor correlation of the incidence of coronary artery disease with the apparent decrease in HDL cholesterol suggested that factor(s) other than HDL cholesterol contributed to the fairly high incidence in the β-adrenoceptor blocker-treated hypertensive subjects of our intervention trial.

This study was supported by the National Research Council for Medical Research, Finland. Liisa Kuhta, Eeva Gustafsson, Helena Ahlroos and Marja Aarnio provided technical and secretarial assistance.

References

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

KANNEL, W.B., CASTELLI, W.P. & GORDON, T. (1979). Cholesterol in the prediction of atherosclerotic disease. *Ann. intern. Med.*, **90,** 85–91.

KRISTENSEN, B.Ø. (1981). Effect of long-term treatment with beta-blocking drugs on plasma lipids and lipoproteins. *Br. med. J.*, **283,** 191–192.

LEHTONEN, A. & VIIKARI, J. (1979). Long-term effect of sotalol on plasma lipids. *Clin. Sci.*, **57,** suppl. 5, 405S–407S.

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

LIPID RESEARCH CLINICS PROGRAM MANUAL OF LABORATORY OPERATIONS (1974). *DHEW Publication No. NIH 75-628.* National Heart and Lung Institute, National Institutes of Health, Bethesda, Md.

MIETTINEN, T.A., HUTTUNEN, J.K., STRANDBERG, T., NAUKKARINEN, V., MATTILA, S. & KUMLIN, T. (1981). Lowered HDL cholesterol and incidence of ischaemic heart disease. *Lancet*, **ii,** 478.

MILLER, N.E., THELLE, D.S., FØRDE, O.H. & MJØS, O.D. (1977). The Tromsø Heart Study. High density lipoprotein and coronary heart disease: a prospective case control study. *Lancet*, **i,** 965–968.

RÖSCHLAU, P., von, BERNT, E. & GRUBER, W. (1974). Enzymatische Bestimmung des Gesamt-Cholesterins im Serum. *Z. Klin. Chem. Klin. Biochem.*, **12,** 403–407.

STREJA, D. & MYMIN, D. (1978). Effect of propranolol on HDL cholesterol concentrations. *Br. med. J.*, **2,** 1495.

TANAKA, N., SAKAGUCHI, K., OSHIGE, K., NIIMURA, T. & KANEHISA, T. (1976). Effect of chronic administration of propranolol on lipoprotein composition. *Metabolism*, **25,** 1071–1075.

WAAL-MANNING, H.J. (1976). Metabolic effects of beta-adrenoceptor blockers. *Drugs*, **11,** suppl. 1, 121–126.