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EFFECT OF PINDOLOL ON SERUM LIPIDS AND LIPID METABOLIZING ENZYMES

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1 The effect on plasma lipids of pindolol given orally over a 6 month period to 20 patients with essential hypertension was studied.

2 During therapy an adipose tissue biopsy was taken from nine patients for the determination of lipoprotein lipase (LPL) activity and serum samples were taken for lecithin cholesterol acyltransferase (LCAT) assays. An additional biopsy and serum samples were taken after a 3 weeks' break in pindolol treatment.

3 Plasma free fatty acid and triglyceride concentrations remained similar during treatment.

4 Plasma total cholesterol was slightly lower ($P < 0.05$) at 6 months than at 1 month.

5 HDL cholesterol concentration and the ratio of HDL to total cholesterol increased slightly, and the increase of HDL cholesterol was significant ($P < 0.05$) at 1 month.

6 LCAT activity was significantly higher ($P < 0.01$) during pindolol treatment than after the break in it. No significant changes in adipose tissue LPL activities were found before and after the break of treatment.

Introduction

Adrenergic β-adrenoceptor blocking drugs play an established part in the treatment of hypertension and ischaemic heart disease. In view of the postulated association between plasma lipids and cardiovascular disease it seems important to investigate beta-blocking agents for their effect on plasma lipids. Many β-adrenoceptor-blockers have been studied in this respect and the general finding is that patients using propranolol (Tanaka *et al.*, 1976), atenolol (Day *et al.*, 1979) and pindolol or metoprolol (Shaw *et al.*, 1978) have a more or less increase in the serum triglyceride level. An increase in the concentration of serum total cholesterol and low density lipoprotein (LDL) cholesterol have been found during treatment with sotalol (Lehtonen & Viikari, 1979) and oxprenolol (Ballantyne *et al.*, 1981). Likewise there are only a few reports on the effect of β-adrenoceptor blocking drugs on high density lipoprotein (HDL) cholesterol. The level of HDL-cholesterol seems to decrease during therapy with propranolol (Helgeland *et al.*, 1978) and sotalol (Lehtonen & Viikari, 1979). Lipoprotein lipase (LPL) and lecithin cholesterol acyltransferase (LCAT) are enzymes participating in lipoprotein metabolism (Tall & Small, 1978; Glomset, 1979). The influences of β-adrenoceptor blocking drugs on serum lipoproteins may be mediated by these enzymes. Pindolol is a non-selective β-adrenoceptor blocking agent with marked intrinsic sympathomimetic activity (ISA).

In the present study we have evaluated the effect of pindolol on serum lipid levels and measured simultaneously the adipose tissue lipoprotein lipase and serum lecithin cholesterol acyltransferease activities.

Methods

Plasma lipids (total cholesterol, HDL-cholesterol, triglycerides and free fatty acids) were measured in a group of 20 hypertensive patients (11 males, 9 females, average age 45.5 years) during 6 months of pindolol treatment. All patients had had no pretreatment at the beginning of the study. Basal lipid estimation was carried out before pindolol (10 mg once daily) was started. The dose of pindolol was increased if necessary to 20 mg once daily to achieve a standing diastolic blood pressure below 90 mmHg.

Fasting plasma lipids were measured at 1, 3 and 6 months. Very-low-density lipoproteins (VLDL) and LDL were precipitated with a polyethylene glycol solution (PEG-6000, final concentration 12%) from fresh plasma, and HDL-cholesterol was determined in the supernatant (Viikari, 1976). During therapy a subcutaneous adipose tissue biopsy of nine patients

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was drawn for the determination of LPL activity. Simultaneously fasting serum samples were taken for lipid determinations and for the LCAT assays. After 3 weeks break of pindolol therapy which occurred 28 weeks after starting therapy, a further biopsy and additional serum samples were taken. The LPL activity was measured from the heparin eluates of adipose tissue using [^{14}C]-triolein (Amersham) mixed with cold trioleylglyceride as a substrate according to Schotz *et al.* (1970) as modified by Hietanen & Greenwood (1977). The LCAT activity was determined by the modified method of Alcindor *et al.* (1978).

Results

The concentration of serum free fatty acids and triglycerides remained about constant during treatment (Table 1). The total serum cholesterol level was slightly lower ($P < 0.05$) after 6 months than after 1 month of therapy.

The concentration of HDL-cholesterol was increased ($P < 0.05$) during the first month of therapy, but there were no significant differences between the level of HDL-cholesterol before therapy and after 3 and 6 months of therapy. The ratio of HDL-cholesterol to total cholesterol increased from 0.18 to 0.20 during therapy, but this increase was not statistically significant.

LCAT activity was significantly higher ($P < 0.01$) during pindolol therapy than after the 3 weeks break of treatment (Table 2). No significant changes in adipose tissue LPL activities were found after discontinuing the drug treatment (Table 2). No significant changes in serum total cholesterol, triglyceride or HDL-cholesterol concentration were found during the drug break. However, the HDL/total cholesterol ratio increased significantly ($P < 0.05$) during the break (Table 2).

Discussion

Many studies (Tanaka *et al.*, 1976; Day *et al.*, 1979; Shaw *et al.*, 1978; Lehtonen & Viikari, 1979) have shown that both nonselective and cardioselective β-adrenoceptor blockers increase the plasma triglyceride levels. It is less clear whether there is a difference in this respect between β-adrenoceptor blockers with or without intrinsic sympathomimetic activity. The results of this study indicate that pindolol does not increase the serum concentrations of triglycerides during 6 months therapy. Shaw *et al.* (1978), found a small but statistically significant increase in serum triglyceride levels after 1 month

Table 1 Plasma lipids during therapy with pindolol

	Concentration (mmol/l)			
	Basal value	*1 month*	*3 months*	*6 months*
Free fatty acids	0.52 ± 0.30	0.60 ± 0.31	0.55 ± 0.30	0.52 ± 0.21
Triglycerides	2.14 ± 1.54	2.27 ± 1.84	2.17 ± 1.24	2.16 ± 1.41
Cholesterol	6.45 ± 1.34	6.61 ± 1.53	6.38 ± 1.07	6.17 ± 1.04°
HDL-cholesterol	1.14 ± 0.35	1.22 ± 0.42*	1.17 ± 0.36	1.18 ± 0.34
$\frac{\text{HDL-cholesterol}}{\text{cholesterol}}$	0.18 ± 0.05	0.19 ± 0.07	0.19 ± 0.05	0.20 ± 0.06

Values are mean ± s.d. The statistical significances have been calculated by the paired *t*-test and have been denoted as follows:
* = $P < 0.05$ between basal and 1 month values
° = $P < 0.05$ between 1 month and 6 months values

Table 2 Plasma lipids, serum lecithin cholesterol acyltransferase (LCAT) activity and adipose tissue lipoprotein lipase (LPL) activity before and after the break of pindolol treatment. For closer details see **Methods** and Table 1

	Cholesterol (mmol/l)	*HDL-cholesterol (mmol/l)*	$\frac{\text{HDL}}{\text{Cholesterol}}$	*Triglycerides (mmol/l)*	*LCAT (as % cholesterol esterified)*	*LPL (μmol g^{-1} h^{-1})*
Pindolol	5.69 ± 1.11	1.04 ± 0.27	0.187 ± 0.05	2.26 ± 1.19	27.1 ± 2.36	0.60 ± 0.24
Break	5.58 ± 1.24	1.08 ± 0.27	0.198 ± 0.05*	1.92 ± 1.08	18.2 ± 4.53**	0.48 ± 0.17

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

therapy with pindolol, and also in our study there was initially a small but not statistically significant increase of triglyceride concentrations. Lehtonen & Viikari (1979) have reported an increase in serum cholesterol and LDL-cholesterol concentration during sotalol treatment, and Ballantyne *et al.* (1981) during oxprenolol therapy. In this study serum cholesterol levels increased during the first month of treatment but this level was statistically significantly lower at 6 months of treatment than at 1 month. The ratio of HDL-cholesterol to total cholesterol is thought to reflect the atherogenicity of serum lipids. β-adrenoceptor-blockers seem to decrease the level of HDL-cholesterol and the ratio of HDL-cholesterol to total cholesterol during long-term treatment (Tanaka *et al.*, 1976; Helgeland *et al.*, 1978; Lehtonen & Viikari, 1979). In this study the level of HDL-cholesterol and the ratio of HDL-cholesterol to total cholesterol increased slightly during pindolol treatment, and the increase of HDL-cholesterol level was statistically significant at 1 month of treatment.

The stimulating effect of catecholamines on lipolysis is mediated by their β-receptor stimulating property. The importance of catecholamines in regulating lipolysis is evident by the fact that administration of β-adrenoceptor blocking drugs will reduce the free fatty acid levels during different lipolytic conditions such as fasting, exercise and following hypoglycaemia (Lager *et al.*, 1979). According to our results pindolol does not reduce the concentrations of serum free fatty acids under resting conditions. In the adipocyte the observed biological response could, in theory, reflect the balance between two opposing actions, β-adrenoceptor blockade and ISA. Comparing the present study with previous reports shows that pindolol has fewer untoward effects on lipid metabolism than β-adrenoceptor blockers without intrinsic sympathomimetic activity.

The present results showed that LPL activity of adipose tissue was not significantly changed, when pindolol treatment was discontinued, and the HDL-cholesterol rose slightly. On the basis of this finding it may be suggested that the decrease of HDL caused by β-adrenoceptor blockers is not mediated by their effects on LPL. Weak negative correlations were obtained between changes in HDL/total cholesterol ratio changes in triglycerides or LPL activity. The LPL degrades triglyceride-rich lipoproteins and transfers surface material to HDL converting HDL_3 to HDL_2 (Taskinen & Nikkilä, 1981).

A marked decrease in the serum LCAT activity was found when pindolol was discontinued. Serum LCAT activity catalyzes the transfer of fatty acids from HDL lecithin to HDL cholesterol during HDL formation (Leiss *et al.*, 1978).

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