PROBUCOL AND HYPERCHOLESTEROLAEMIA

Addition of drug therapy to a low animal fat diet is often required in the control of hypercholesterolaemia. None of the standard drugs is entirely satisfactory. The very effective bile acid resins are often poorly tolerated. Clofibrate is palatable but has the major drawback of inducing an increase in biliary cholesterol which persists throughout treatment (Bateson, Maclean, Ross & Bouchier, 1978; Angelin, Einarsson & Leijdt, 1979). As a result it markedly increases cholesterol gallstone prevalence (Bateson *et al.*, 1978) and the cholecystectomy rate (Coronary Drug Project Research Group, 1975; Oliver, Head, Morris & Cooper, 1978). Its usefulness in protecting from ischaemic heart disease is also doubtful (Coronary Drug Project Research Group, 1975; Oliver *et al.*, 1978). A lesser degree of lithogenicity is associated with nicotinic acid treatment (Angelin *et al.*, 1979).

Probucol is an alternative (well-tolerated) preparation recently introduced in Britain. The purpose of this study was to evaluate the effect of probucol on biliary lipids, and hence the likelihood of gallstone induction during therapy for hypercholesterolaemia.

Twelve consecutive adult patients with primary hypercholesterolaemia (>7.8 mmol/l; WHO Types IIa and IIb) not completely responsive to low animal fat diet agreed to participate. This study was approved by the Ethics Committee of the Tayside Health Board. There were five men and seven women, aged 30–66 (median 50) years. Four patients had familial hypercholesterolaemia and a further two had a family history of premature ischaemic heart

disease. Ten patients had ischaemic heart disease and another had intermittent claudication. All had received individual dietary advice. Ten had been on a low animal fat diet for 3–61 (median 31) months. The other two had been on such a diet for 16 and 17 years respectively. Diet was maintained throughout the study. Five patients had been resistant to other hypolipidaemic drugs, four had responded to clofibrate which had been discontinued and the other three had never had specific drug therapy.

Three patients continued stable anti-hypertensive and diuretic therapy. Glycerine trinitrate was allowed as required. No other drugs were permitted for at least 1 month before or during the study.

All patients underwent oral cholecystography, and all 12 had normally functioning gallbladders. Duodenal drainage after i.v. CCK was performed on fasting patients. Biliary lipid analysis was conducted as described previously (Bateson, Ross, Murison & Bouchier, 1977) with immediate Folch extraction for phospholipid estimation. Blood was taken for serum lipids. Total serum cholesterol and triglycerides were measured enzymatically on a Technicon Auto-analyzer II. High density lipoprotein cholesterol (HDL-cholesterol) was similarly measured after sodium phosphotungstate-magnesium precipitation (Lopes-Virella, Stone, Ellis & Colwell, 1977). Probucol 500 mg twice daily was started, and patients were seen at monthly intervals for clinical assessment and repeat blood tests. The tablets were dispensed by the supervising physician and the patients were asked to produce the empty bottles for inspection. After

Table 1 Biliary lipids before (B) and after (A) probucol 1 g daily for 3 months

Age (years)	Sex	Body mass index	Phospholipids (mol %)		Bile salts (mol %)	Cholesterol (mol %)	Saturation index	Lithogenic index
66	F	26.2	B	18.9	75.5	5.5	0.56	0.91
			A	46.0	46.7	7.3	1.19	1.19
46	M	23.9	B	9.5	85.7	4.8	0.60	1.22
			A	25.1	71.1	3.8	0.38	0.54
40	M	24.4	B	8.2	87.8	4.0	0.52	1.07
			A	21.2	75.3	3.5	0.35	0.55
45	M	19.3	B	13.2	84.7	2.1	0.24	0.47
			A	17.0	79.4	3.6	0.38	0.66
51	F	21.5	B	10.5	86.1	3.4	0.42	0.84
			A	20.7	75.1	4.3	0.43	0.68
44	M	31.2	B	39.3	54.2	6.5	0.78	0.78
			A	25.8	68.9	5.3	0.53	0.72
		Mean	B	16.6	79.0	4.4	0.52	0.88
				±4.8	±5.3	±.6	±.07	±.11
		Mean	A	26.0	69.4	4.6	0.54	0.72
				±4.2	±4.8	±.6	±.13	±.10
			NS	NS	NS	NS	NS	

3 months of treatment duodenal intubation was repeated. The blood tests were again repeated after 4 and 6 months' therapy.

All results are presented as means $\pm$ s.e. mean. Differences in serum triglycerides and biliary bile acids were examined by the Wilcoxon paired sample test. Other differences were examined by the Student's *t*-test.

Probucol was well tolerated. Mean body weight did not change significantly after diet treatment or during probucol therapy.

Analyses of paired samples of bile-rich duodenal aspirate were available in six patients (Table 1). There were no significant changes in the molar percentage concentrations of phospholipids, cholesterol, and total bile acids; nor in the saturation of lithogenic indices (Thomas & Hofmann, 1973). The proportion of secondary bile acids (deoxycholic + lithocholic acids) increased (13.9 ± 2.6 to 20.0 ± 3.5 mol%, $P < 0.05$), largely because of a rise in the proportion of deoxycholic acid. No other change in the distribution of bile acids was noted.

The average serum total cholesterol in all twelve patients before any treatment was 10.7 ± 0.5 mmol/l, falling after diet alone to 9.9 ± 0.5 mmol/l (7.5%, NS). During probucol therapy there was a further fall in mean serum total cholesterol of 5–10% (Table 2). There was an individual variation in the response of serum cholesterol, and in one patient the level rose after treatment; it was never lower than the pre-treatment value of 11.0 mmol/l and at the end of 6 months serum cholesterol was 14.5 mmol/l. She was clearly unusual, and in clinical practice would not have been continued on therapy. There was otherwise no difference between men and women in the average serum lipid response to probucol, and for the other patients a persistent reduction from the diet-treated total serum cholesterol level was detected at both 4 months (8.7 ± 0.4 mmol/l) and at 6 months (8.6 ± 0.4 mmol/l). Calculation (Friedewald, Levy & Frederickson, 1972) showed the reduction in serum total cholesterol to be mainly due to a fall in LDL-cholesterol.

There was an immediate, more marked, and sustained fall in HDL-cholesterol in every patient during each of the first 3 months, with a consequent reduction in HDL/total cholesterol ration (Table 2). Serum HDL-cholesterol later showed a trend to rise again towards the diet-treated mean value. At 4 months mean serum HDL-cholesterol was 0.76 ± 0.6 mmol/l ($P < 0.025$). It was 0.85 ± 0.7 mmol/l at 6 months (NS). The mean HDL/total cholesterol ratio at 6 months ($10.1 \pm 1.0\%$) was similar to the value before probucol therapy.

This short-term study showed that probucol did not influence biliary lipid values in patients treated for hypercholesterolaemia, and there was no deterioration in biliary cholesterol content or saturation. The mechanism of action for probucol remains speculative, but it does not produce an isolated increase in biliary cholesterol secretion and, therefore, therapy with this agent should not be associated with an increased prevalence of cholesterol gallstones.

The striking early reduction of HDL-cholesterol which we have observed is consistent with the findings of others (Heel, Brogden, Speight & Avery, 1978). As probucol did not improve the HDL/total cholesterol ratio it seems to have a limited potential for correcting disordered lipid metabolism. It should probably be treated as a reserve drug for individual patients resistant to diet and other drugs, and monitoring of HDL-cholesterol is important during therapy.

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Table 2 Serum lipids (mmol/l) of ten patients receiving probucol 1 g daily

	Months of therapy			
	0	1	2	3
Total cholesterol	9.9 ± 0.5	9.4 ± 0.5	$8.9 \pm 0.3^{**}$	$9.1 \pm 0.4^*$
Triglycerides	2.0 ± 0.2	2.2 ± 0.2	2.4 ± 0.4	$1.5 \pm 0.1^*$
HDL-cholesterol	0.93 ± 0.07	$0.71 \pm 0.08^{***}$	$0.72 \pm 0.07^{***}$	$0.74 \pm 0.06^{***}$
HDL/Total cholesterol %	9.3 ± 0.9	$7.9 \pm 1.1^{***}$	$8.4 \pm 1.0^{**}$	$8.3 \pm 0.7^*$

* $P < 0.05$ values on diet alone (month 0).

** $P < 0.01$ values on diet alone.

*** $P < 0.001$ values on diet alone.

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THEOPHYLLINE CONCENTRATION IN SALIVA AS A GUIDE FOR INDIVIDUALIZATION OF ITS THERAPEUTIC USE

Marked interindividual differences have been found in theophylline metabolism in man (Mitenko & Ogilvie, 1973; Piafsky, Sitar, Rangno & Ogilvie, 1977; Plavsic, Bakran & Vrhovac, 1978). It is necessary to individualize treatment with drugs which demonstrate great interindividual variations in pharmacokinetic parameters (Bonora, Ottoboni, Guaglio, Terzoni & Rondanelli, 1980; Chiou, Huang & Huang, 1980; Walther, Meyer, Quedrow, Lenscher, Kohler & Herenburg, 1978). The possibility of using saliva samples for monitoring theophylline treatment has been studied in recent years (Breimer & Danhof, 1980; Horning, Brown, Nowlin, Lartratanangkoon, Kellaway & Zion, 1977). Some authors have found a good correlation between

saliva and serum concentrations of theophylline (Breimer & Danhof, 1980; Horning *et al.*, 1977), but others disagree (Boobis, Trembath, Chambers, Edmunds & Carswell, 1979). It has been shown that concentrations in saliva for weak acidic and basic drugs are equivalent to their free fraction in the serum (Mucklow, Bending, Kahn & Dollery, 1978). Although small interindividual variations in the volume of distribution exist, differences in biological half-lives of theophylline are more important from a clinical point of view (Mitenko & Ogilvie, 1973; Piafsky *et al.*, 1977). The accuracy of the calculation of the biological half-life is dependent upon the number of samples used. In the β -phase of elimination at least three determinations are desirable, but it has been shown that determination of two well-chosen samples may be sufficient (Bonora *et al.*, 1980; Chiou *et al.*, 1980). We have evaluated this for theophylline.

Ten healthy volunteers were fasted overnight and abstained from smoking and caffeine containing drinks during the study. Intravenous aminophylline in a dose of 6 mg/kg was administered over a period of 15 min. Blood (2 ml) and saliva (1 ml) samples were obtained 3 and 6 h after starting the infusion. Each subject's mouth was rinsed and then each chewed parafilm for 5 min before taking saliva. Serum and salivary theophylline concentrations were determined by the RIA method (GammaDab ^{125}I theophylline radioimmunoassay kit, Clinical Assay). Biological half-lives were calculated from the relation $C_2 = C_1 e^{-K_e(t_2-t_1)}$, where C_1 and C_2 are theophylline concentrations in the time t_1 and t_2 after the dose

Figure 1 Correlation between theophylline concentrations in simultaneous serum and saliva samples. $C_{\text{saliva}} = 0.8 + 0.38 C_{\text{serum}}$, $r = 0.93$.