A COMPARISON OF CHOLESTYRAMINE AND NICOTINIC ACID IN THE TREATMENT OF FAMILIAL TYPE II HYPERLIPOPROTEINAEMIA

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- 1 The effects of cholestyramine and nicotinic acid on plasma lipid concentration have been compared in patients with type IIa hyperlipoproteinaemia.
- 2 During a 3-month period, cholestyramine resulted in a mean decrease in cholesterol levels of 26%. Triglyceride levels rose in eight of the ten patients during treatment with this drug but in the majority of patients remained within the normal range.
- 3 During nicotinic acid therapy, cholesterol fell by a mean of 21% and triglyceride by a mean of 23%.
- 4 The slow release preparation of nicotinic acid used was acceptable to the majority of the patients studied and the results therefore suggest that this drug may be a useful alternative to the more widely used agent, cholestyramine.

Introduction

Type II hyperlipoproteinaemia is characterized either by an increase in the low density lipoprotein fraction (LDL) alone or by an increase in both the LDL and the very low density lipoprotein fraction (VLDL). The former disorder has been classified by the World Health Organization (WHO) as type IIa, in which the plasma cholesterol is increased, and the latter as type IIb, in which both plasma cholesterol and triglyceride concentrations are increased (World Health Organization, 1971). Both types are associated with an increased risk of ischaemic heart disease (Carlson & Bottiger, 1972). Cholestyramine, in conjunction with a cholesterol-lowering diet, is widely recommended as the treatment of choice if diet therapy alone is unable to control cholesterol levels (Levy, Morganroth & Rifkind, 1974; Lewis, 1975). By binding bile acids in the bowel and preventing their reabsorption, this drug usually produces a decrease in LDL levels by 20–40% (Lewis, 1975), although it may increase levels of VLDL (Levy *et al.*, 1974). Nicotinic acid therapy has been reported to decrease the plasma level of both these lipoprotein fractions (Levy *et al.*, 1974), but has not not been as widely used as cholestyramine because of the side effects when the drug is given in the doses required to produce a lipid-lowering effect. Olsson, Oro & Rossner (1974) have used a slow release form of nicotinic acid which produces a satisfactory response in a variety of hyperlipoproteinaemias and has remarkably few side effects (Olsson *et al.*, 1974).

We report here the results of a clinical trial comparing the effectiveness of the two drugs as hypolipidaemic agents in primary type IIa hyperlipoproteinaemia.

Methods

All patients under the age of 64 years who presented to the Lipid Clinic at the Radcliffe Infirmary with plasma cholesterol levels between 7.77 and 11.66 mmol/l during the period September, 1974 to May, 1975, were considered potentially suitable for the trial, provided they had not previously received lipid-lowering therapy and lived within easy travelling distance of the hospital. Patients with secondary hyperlipoproteinaemia, pregnant women, and patients with severe intercurrent illness, were excluded. A diet which was low in cholesterol (below 300 mg/day), relatively high in polyunsaturated fat (P:S ratio, 1.5:1), and adjusted to suit individual energy requirements, was recommended to each patient. Drug therapy was considered necessary if, after 3 months on this dietary regimen, the plasma cholesterol concentration had not fallen below 7.77 mmol/l. Informed consent for the drug trial was obtained from 11 patients with heterozygous familial type IIa hyperlipoproteinaemia.

All patients were known to have at least one affected first degree relative. Patients 1–3 were a

mother and two children. Patients 7 and 8 were brothers, and patients 9 and 10 were a mother and son. Patient 6 had had a myocardial infarction 12 months before the start of the trial, patient 9 a mild cerebral thrombosis 9 months previously, and patient 7 suffered from epilepsy. The rest were clinically free from disease and had normal electrocardiographs and chest X-rays. Tendon xanthomata were present in patients 1, 7, 8, 9 and 11.

Patients were randomized into one of the two treatment groups, cholestyramine (Questran, Bristol Laboratories, 4 g four times daily) and nicotinic acid (Nicangin, Astra Chemicals, 1 g three times daily). The patients were advised to take nicotinic acid at meal times and were asked to continue to follow the dietary advice throughout the trial. The dose of both drugs was increased gradually until the maximum was reached after 6 days. Patients were seen at 2-weekly intervals and fasting blood samples taken at each visit. Therapy was stopped after a 12-week period. When the plasma cholesterol had increased to the pre-treatment levels (usually after a period of from 6–12 weeks) the alternative therapy was commenced and continued for a further 12-week period.

At each visit information was obtained concerning side effects of the drugs, and blood counts and plasma cholesterol (Searcy & Bergquist, 1960) and triglyceride (Eggstein & Kreutz, 1966) estimations were performed on blood samples collected after a 14-hour overnight fast. Lipoprotein electrophoresis (Noble, 1968) was performed on the initial blood sample to confirm the WHO type. Serum bilirubin and SGOT estimations were carried out monthly. The significance of the differences between changes in the plasma lipids

on the two treatment groups was tested by the Wilcoxon test.

Results

Plasma cholesterol and triglyceride concentration before and during the two treatment regimens are given in Tables 1 and 2. Patient 4, who had commenced the trial on nicotinic acid therapy, and patients 7 and 8, who had started with cholestyramine, found the alternative drug unacceptable and refused to continue therapy.

A fall in plasma cholesterol occurred in every patient on both cholestyramine and nicotinic acid therapy. The mean percentage fall during treatment with cholestyramine was 26% and 21% on nicotinic acid. This difference in the responses to the two forms of treatment was not statistically significant. The plasma triglyceride levels fell in all but one patient during nicotinic acid therapy and increased in all but two patients during treatment with cholestyramine. In none of the patients was there any appreciable tendency for the early changes to become less marked towards the end of the trial period. The body weights fluctuated during the period of the trial but no significant changes took place during either treatment.

During treatment with cholestyramine, four patients experienced slight constipation or abdominal discomfort, and patient 4 refused to continue the drug after 8 weeks for this reason. He had started the trial on nicotinic acid and had probably not taken cholestyramine regularly even during the 8-week period. On nicotinic acid therapy, six patients

Table 1 Cholesterol levels (mmol/l) before and during treatment with cholestyramine and nicotinic acid

Patient number (sex and age)	Cholestyramine		Nicotinic acid	
	Cholesterol level (mmol/l)			
	Pre-treatment*	Mean during treatment† (and % change)	Pre-treatment*	Mean during treatment† (and % change)
1 (F, 45)	8.63	6.94 (−20)	9.25	7.56 (−18)
2 (F, 16)	7.85	5.91 (−25)	8.39	5.47 (−35)
3 (M, 12)	8.39	6.45 (−23)	8.01	6.35 (−21)
4 (M, 21)	Discontinued after 8 weeks		8.94	6.66 (−26)
5 (F, 18)	8.81	6.48 (−27)	7.98	6.17 (−23)
6 (M, 37)	9.12	6.22 (−32)	8.73	6.76 (−23)
7 (M, 27)	9.82	7.46 (−24)	Discontinued after 4 weeks	
8 (M, 30)	10.16	6.06 (−40)	Discontinued after 6 weeks	
9 (F, 50)	8.78	7.02 (−20)	9.87	8.81 (−11)
10 (M, 23)	10.75	8.58 (−20)	10.10	9.35 (−7)
11 (M, 54)	10.60	6.97 (−34)	9.95	7.85 (−21)
Mean	9.29	6.81 (−27)	9.02	7.23 (−21)

* Mean of at least three measurements taken at weekly intervals.

† Mean of six measurements taken at two-weekly intervals during treatment.

experienced some flushing and two found it unacceptable for this reason. Two patients experienced mild nausea and diarrhoea which was temporary and did not necessitate discontinuing therapy.

Liver function tests remained unaltered during the period of the trial. Three patients had a neutrophil count between 790 and 1,892 per mm³ on one occasion while taking nicotinic acid, but in each case a blood count repeated within a few days showed a neutrophil count of above 3,000 per mm³ despite continued administration of the drug.

At the conclusion of the trial, when the patients were asked to choose which of the agents they would prefer for long term maintenance, six selected nicotinic acid, and five cholestyramine. It has been possible to follow six of these patients for varying periods. Patients 7, 8 and 11, who selected cholestyramine, now have cholesterol levels of 7.6, 4.8 and 7.5 mmol/l, 7, 9 and 4 months respectively after the conclusion of the trial. Their triglyceride levels are 1.32, 0.78 and 1.12 mmol/l respectively. Patients 6 and 9 selected nicotinic acid and their cholesterol levels are 6.9 and 7.4 mmol/l, 15 and 8 months later. Triglycerides are 0.98 and 0.52 mmol/l. Patient 10 also selected nicotinic acid, but because his lipid levels were not considered to be satisfactorily controlled, clofibrate (1 g, twice daily) was added to the treatment. Now, 7 months after commencement of this combination treatment, his cholesterol is 7.3 mmol/l and triglyceride 1.12 mmol/l.

Discussion

Despite the relatively small number of patients studied, use of a crossover design after random allocation permits reasonably confident conclusions to be drawn from this study. The slow release preparation of nicotinic acid was nearly as effective in lowering plasma cholesterol in type II hyperlipoproteinaemia as the more widely used preparation, cholestyramine. Most patients were able to tolerate both drugs well and similar numbers of patients had a preference for each drug at the termination of the trial. Although the plasma triglycerides increased on cholestyramine, the levels remained within the normal range in all but one of the patients, and the increase may not be of clinical significance. Other workers have reported variable triglyceride responses in patients with type II on cholestyramine alone, and a consistent fall in levels of this lipid when clofibrate is added (Levy *et al.*, 1974; Oro, Olsson, Rossner & Carlsson, 1975).

There is relatively little information concerning the long term efficacy of these drugs. There is evidence that the lipid-lowering action of cholestyramine is sustained (West, Fasbrooke, & Lloyd, 1975). The opportunity we have had of following a number of the patients after the conclusion of the trial provides some data concerning nicotinic acid but clearly much more information is required. The results do, however, suggest that while cholestyramine may remain the

Table 2 Triglyceride levels (mmol/l) before and during treatment with cholestyramine and nicotinic acid

	Cholestyramine		Nicotinic acid	
	Triglyceride level (mmol/l)			
Patient number (sex and age)	Pre-treatment*	Mean during treatment† (and % change)	Pre-treatment*	Mean during treatment† (and % change)
1 (F, 45)	1.05	1.27 (+20)	1.28	1.07 (−16)
2 (F, 16)	0.53	0.68 (+28)	0.66	0.45 (−31)
3 (M, 12)	0.85	1.04 (+23)	0.73	0.55 (−25)
4 (M, 21)	0.76	Discontinued after 8 weeks	0.68	0.63 (−7)
5 (F, 18)	1.07		1.01	0.44 (−56)
6 (M, 37)	1.67	2.25 (+34)	1.92	1.55 (−19)
7 (M, 27)	1.37	0.95 (−31)	Discontinued after 4 weeks Discontinued after 6 weeks	
8 (M, 30)	0.89	1.34 (+51)		
9 (F, 50)	0.84	0.95 (+14)	1.20	0.53 (−56)
10 (M, 23)	0.97	2.03 (+169)	1.38	1.75 (+27)
11 (M, 54)	0.81	0.77 (−6)	1.24	0.77 (−41)
Mean	1.01	1.28 (+28)	1.01	0.86 (−23)

* Mean of at least three measurements taken at weekly intervals.

† Mean of six measurements taken at two-weekly intervals during treatment.

treatment of choice in patients with type IIa, and can be used alone or in conjunction with clofibrate in type IIb, nicotinic acid does provide a satisfactory alternative. In view of the consistent fall in plasma triglyceride levels, nicotinic acid may be of particular value in patients with type IIb.

Nicotinic acid inhibits adipose tissue lipolysis and the fall in VLDL is thought to be secondary to decreased flux of free fatty acids (Levy *et al.*, 1974). Decreased production of LDL from VLDL may explain the fall in cholesterol levels. The mechanism of action of nicotinic acid has recently been investigated in monkeys (Magide, Myant & Reichl, 1975). Subcutaneous injections of nicotinic acid lowered both plasma VLDL and LDL concentrations and diminished incorporation of [14 C]-threonine into VLDL and LDL apoproteins. However, the cholesterol-lowering mechanism of nicotinic acid may be complex since some of the circulating apo-B of

LDL is derived from sources other than circulating VLDL. The different modes of action of nicotinic acid and cholestyramine suggest that combination therapy may be helpful in resistant cases and Moutafis, Myant, Marcini & Oriente (1971) have demonstrated this in four cases of homozygous familial type II hyperlipoproteinaemia (Moutafis *et al.*, 1971). Clofibrate and nicotinic acid also appear to be a useful combination of drugs. In addition to the one patient in this series, we have successfully treated three other resistant cases in this way.

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