A Long-term Trial of Gemfibrozil in the Treatment of Hyperlipidæmias

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The purpose of the present study was to evaluate the serum lipid lowering effect of gemfibrozil in long-term treatment.

Patients and Methods

A total of 34 subjects with primary hyperlipidæmia were treated with gemfibrozil for six months or more. The subjects were considered to be hyperlipidæmic if they had either serum fasting levels of cholesterol above 7.75 mmol/l, triglycerides above 2.25 mmol/l, or both. The cohort comprised 19 males and 15 females. Ages varied from 19 years to 71 years, the mean being 51.5 years. Four patients had xanthomas, 2 had electrocardiographic evidence of myocardial infarction, 1 had left bundle branch block and 1 right bundle branch block. Two patients had a history of angina of effort.

In addition to serum lipids, physical examination and laboratory tests including ESR (Westergren), hæmoglobin, hæmatocrit, red and white cell counts, and serum GPT, urinalysis and ECG were performed to observe any side effects. Secondary hyperlipidæmias were excluded by clinical examination and the appropriate laboratory tests.

The subjects were first treated with placebo for four weeks. During this time serum lipids were determined three times (Days 1, 14 and 28), and the mean of these measurements was used as the non-treatment value.

After the placebo period, active treatment with gemfibrozil at 800 mg daily was begun, the daily dose being given in two equal portions. The control visits occurred at four-weekly intervals. During these visits samples were taken for monitoring serum lipids and GPT, ESR, hæmatocrit, white cell count and for doing a urinalysis.

Table 1

Effect of gemfibrozil in lowering serum cholesterol

	Cholesterol response (%)		
Fall	*After 1 month*	*After 6 months*	*After 12 months*
0–10%	10 (1)	8 (—)	7 (1)
11–21%	13 (6)	15 (5)	5 (3)
>21%	8 (5)	8 (6)	3 (3)
Total	31 (12)	31 (11)	15 (7)

Numbers of patients with a fall of serum cholesterol below 7.75 mmol/l shown in parentheses

The subjects were weighed and enquiries were made about any adverse reactions. They were instructed to continue their normal day-to-day habits as far as possible, especially those relating to food intake, physical activity and smoking. If an adequate reduction in serum lipids was not evident after three months, the dose of gemfibrozil was progressively increased to a maximum daily dose of 1600 mg.

All laboratory determinations were carried out after overnight fasting. Serum triglycerides were determined by the Auto Analyzer method, cholesterol according to Pearson *et al.* (1953). The method of Noble (1968) was modified for the determination of serum lipoproteins by agarose gel electrophoresis. Total lipids were determined according to Zöllner & Kirsch (1962). Boehringer reagent kits were used for the determination of serum GPT, alkaline phosphatase and CK.

The mean serum cholesterol concentration measured before the active treatment period was above 7.75 mmol/l in 31 subjects. Ten subjects had serum triglyceride levels above 2.25 mmol/l. The initial non-treatment cholesterol concentration varied between 7.8 and 12.9 mmol/l, the mean being 9.53 mmol/l. The non-treatment triglyceride values varied from 0.8 mmol/l to 11.2 mmol/l with a mean of 2.51 mmol/l. When classified according to Fredrickson types, 25 subjects belonged to type IIa, 2 to IIb, 2 to 'floating III', and 2 to type IV.

Results

Serum cholesterol: After one month of treatment, the cholesterol level was decreased more than 10% in 21 subjects out of 31, and in 12 the serum cholesterol was below 7.75 mmol/l (Table 1). While one month of treatment showed a decreased trend in serum cholesterol, a more pronounced effect was seen after three months (Fig 1). From the values obtained at three months, it can be seen that there are patients who remained resistant, with a minimal change, if any, in serum cholesterol. The increase of the dose of gemfibrozil to 1200 mg after three months of treatment resulted in a more pronounced hypocholesterolæmic effect (Fig 2) in most subjects. This hypolipidæmic action of gemfibrozil seems to be sustained (Fig 3).

After six months of treatment, the serum cholesterol was below 7.75 mmol/l in 11 out of 31 subjects. In addition there were 8 subjects with a reduction of less than 10%. In 23 subjects the decrease was more than 10%, in 8 of whom it was more than 21% (Table 1). After one year the serum cholesterol was below 7.75 mmol/l in 7 subjects out of 15. The reduction was more than 10% in 8, in 3 of whom it was more than 21%, but in 7 it was less than 10%. Those who failed to

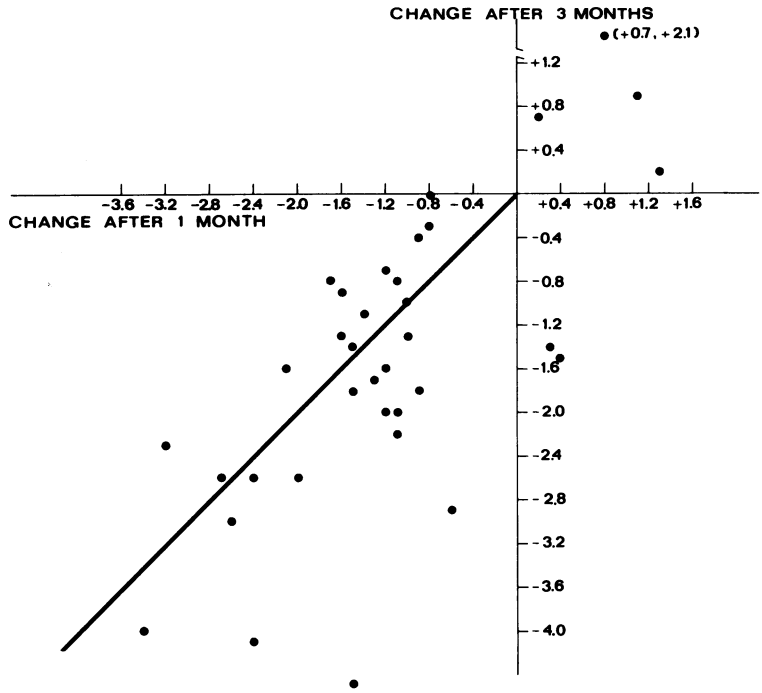

Fig 1 *Correlation of serum cholesterol values (mmol/l) between treatments for one month and three months*

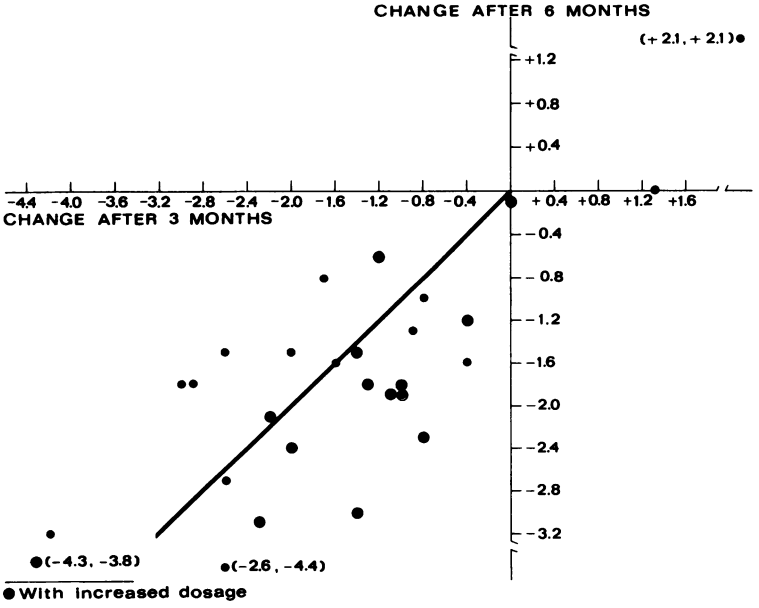

Fig 2 *Correlation of serum cholesterol values (mmol/l) between treatments for three months and six months*

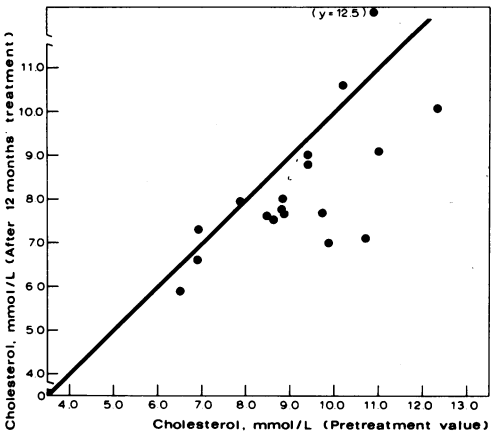

Fig 3 *Correlations between pretreatment serum cholesterol values and those after treatment for 12 months*

respond belonged to type IIa and most had a family history of hypercholesterolæmia.

Reduction in serum cholesterol values in a family consisting of mother (51 years), daughter (20 years) and son (19 years) is shown in Fig 4. The respective initial pretreatment values were 12.9 mmol/l, 10.9 mmol/l and 10.6 mmol/l. It can be seen that the cholesterol was initially decreased in all of them. During the course of the trial, however, only the 20-year-old daughter maintained a low level of serum cholesterol. The role played by sex and age in the response of the individual family members needs further investigation.

Serum triglycerides: The fall of serum triglyceride levels during treatment with gemfibrozil was clearer than that of cholesterol (Fig 5). A total of

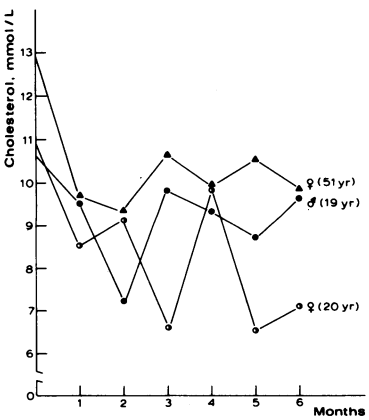

Fig 4 *Serum cholesterol values during treatment for six months in a family consisting of mother (51 years), daughter (20 years) and son (19 years)*

10 subjects had initial levels above 2.25 mmol/l. After treatment for one month the levels were decreased by more than 35% in 8 subjects and 6 of them achieved normal levels. The effect was sustained for the next five months. In 8 subjects treated for one year, all but 3 showed a fall in serum triglycerides of more than 35% from the pretreatment values.

Lipoprotein electrophoresis: Lipoprotein electrophoresis was carried out in 11 type IIa subjects twice during the pretreatment period, and after six months' treatment with gemfibrozil (Table 2). There was a clear reduction in the concentration of the beta-lipoprotein fraction in all subjects, and the mean value decreased from 6.93 g/l to 5.37 g/l. The pre-beta and alpha-lipoprotein fractions remained virtually unchanged throughout the trial.

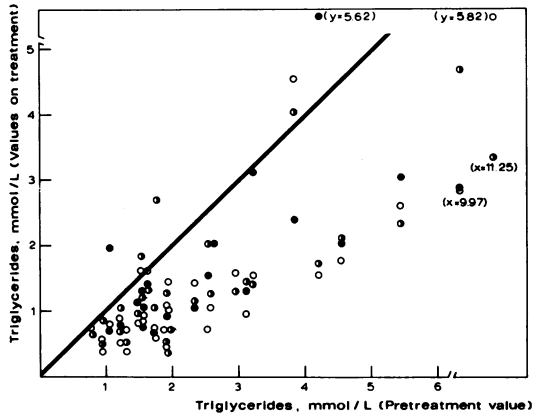

Fig 5 *Correlation between pretreatment triglyceride values and those after the treatment.* ○ *treated for one month,* ◑ *for six months, and* ● *for 12 months*

Concentrations were normal even in the non-treatment period, and so reductions were not necessarily desirable in their case. Most of the fall in the triglyceride levels in these type IIa subjects seems to have been associated with the decreased beta-lipoprotein, as was the fall in the serum cholesterol level.

Tolerance: Gemfibrozil was well tolerated in all subjects participating in the trial. None dropped out because of the drug. Neither serum GPT, hæmatology nor urinalysis indicated any evidence of side effects or organ toxicity. The subjects were free from subjective side effects associated with the drug; this was also evident from the fact that all wished to continue the trial.

Weight of the subjects: The weight of the subjects varied within 2 kg during the trial with 2 exceptions, 1 subject gained 4 kg and 1 lost 5 kg.

Table 2

Concentrations of serum lipids and lipoproteins in 11 subjects during the pretreatment period and after treatment for six months

Patient No.	*Control period*					*After treatment for six months*				
	Beta	*Pre-beta*	*Alpha*	*TG*	*Chol*	*Beta*	*Pre-beta*	*Alpha*	*TG*	*Chol*
1	5.9	1.2	2.7	1.9	9.0	4.0	1.6	2.4	1.2	8.4
2	6.5	1.4	1.7	0.8	10.7	4.6	0.9	2.2	0.7	8.6
3	6.7	0.6	2.5	0.9	10.2	4.4	0.9	2.9	0.6	8.3
4	6.9	0.9	1.5	0.9	10.8	6.3	0.7	2.3	0.9	8.5
5	6.4	0.8	2.6	0.9	10.8	6.0	0.6	2.8	0.8	8.5
6	8.9	0.5	1.9	1.4	12.9	8.5	0.6	0.6	1.1	9.8
7	8.0	1.1	1.8	1.3	10.6	7.2	0.9	2.3	0.9	9.6
8	8.2	0.5	1.9	0.9	10.9	6.3	0.5	1.5	0.4	7.1
9	7.8	1.0	1.5	1.9	10.0	4.4	0.8	2.0	0.8	8.3
10	5.9	1.3	2.5	1.5	9.0	4.4	1.5	2.1	1.5	7.9
11	4.9	1.0	3.0	0.8	8.6	3.7	1.1	2.4	0.6	7.2
Mean	6.93	0.94	2.15	1.20	10.3	5.37	0.92	2.14	0.86	8.36

Lipoprotein concentrations are expressed as g/l; those of cholesterol and triglycerides as mmol/l. Normal values for the individual lipoprotein species, based on analysis of 40 healthy subjects, were: beta 1.7–3.5 g/l, pre-beta 0.4–1.4 g/l, and alpha 1.2–2.4 g/l.
TG, triglycerides
Chol, cholesterol

Conclusions

The results of this long-term trial warrant consideration of gemfibrozil as an effective lipid lowering agent. The failure of some patients to respond does not weaken the claim. From the practical point of view, the classification of hyperlipidæmias into different subtypes has contributed to the understanding of their pathogenesis. However, much remains unresolved.

In the practical situation of treating patients, the value of this precise classification, cumbersome and not always completely accurate as it is, has been questioned, even by Fredrickson (1972). The reason is that the efficacy of an agent cannot be predicted for all patients even when there is a tendency for certain hypolipidæmic agents to be more effective in certain types of hyperlipidæmias. We lack the knowledge of the pathogenesis of the hyperlipidæmias and the mode of action of the lipid lowering agents. There can be no certainty in any case about the complete effectiveness of a drug, until it has been tried.

The treatment of hyperlipidæmia is often tailor-made to the individual. Experience is of great value in finding the most suitable agent. Long-term trials of an agent with a variety of subjects are also very necessary. The lipid lowering effect of gemfibrozil seems to be more pronounced for triglycerides than for cholesterol. However, both cholesterol and the beta-lipoproteins are decreased, indicating that not only subjects with high triglycerides and pre-beta lipoproteins, but also those with high cholesterol and beta-lipoproteins may benefit from the hypolipidæmic action of gemfibrozil. From the practical point of view, gemfibrozil has two very important characteristics in the treatment of hyperlipidæmias: it is free of side effects and its effect is sustained.

Acknowledgment

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