Session II
Clinical Studies of Lipid Levels

Chairman Professor E A Nikkilä

Effect of Gemfibrozil on Lipoprotein Concentrations in Different Types of Hyperlipoproteinæmia

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The short-term effects of gemfibrozil on lipoprotein concentrations in hyperlipoproteinæmia (HLP) were reported by Olsson & Carlson (1975*a*). The purpose of the present study was to evaluate the effect of the compound when given over a 24-week period.

Materials and Method

Thirty-four subjects (including 27 males) with primary HLP and a mean age of 54 years took part in the study. Most of the subjects had experienced atherosclerotic manifestations, for example, myocardial infarction. Long before the study all subjects had been advised to have a diet low in saturated fat and high in polyunsaturated fats and to restrict their total caloric intake. No subjects were treated with anticoagulants, insulin, oral antidiabetics, œstrogens, oral contraceptives, thyroid or antithyroid medication.

After a pretreatment period, including three serum lipid determinations at least one month apart, the patients were treated with 400 mg of gemfibrozil twice daily for 24 weeks. Determinations of cholesterol (Block *et al.* 1965) and triglycerides (TG) (Kessler & Lederer 1966) were performed every fourth week and lipoprotein determinations were carried out immediately before the start of treatment and after four, 12 and 24 weeks.

The following parameters were measured every fourth week according to the hospital routine: body weight, hæmoglobin concentration, hæmatocrit, white blood cell count, differential count, platelet count, erythrocyte sedimentation rate, blood sugar, alkaline phosphatase, S-ALAT and S-ASAT and serum uric acid levels, and urine analysis was performed for protein, sugar and ketones.

Serum lipoproteins were analysed as described by Carlson (1973). In the typing of HLP, cut-off points were used as described previously (Beaumont *et al.* 1970, Olsson & Carlson 1975*b*).

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The sera of the subjects were typed as follows: type IIa, 5; type IIb, 3; type III, 3; type IV, 23.

Results

Side effects and drop-outs: Eight subjects had to stop treatment, 4 because of intercurrent illness (myocardial infarction 2, diabetes 1, and gall bladder disease 1). Two subjects were excluded because of lack of cooperation.

Two subjects had to stop treatment as a result of side effects attributable to the drug, 1 because of nausea and 1 because of abdominal pain. These symptoms recurred when the drug was given for a second time.

No chemical or hæmatological abnormalities attributable to the administration of gemfibrozil were noted.

Mean body weights remained unchanged throughout the study.

Serum lipids (Tables 1 and 2) and lipoproteins (Tables 3 and 4): Serum total TG increased in all types of HLP. In types III and IV, HLP decrease was pronounced, approximately 40%.

Serum cholesterol also decreased in all types of HLP, particularly in types IIa and IIb, where the decrease was 20–25%.

Table 1

Plasma triglyceride (TG) concentrations (mmol/l) in different types of hyperlipoproteinaemia (HLP) before and during treatment with gemfibrozil (400 mg twice daily)

			Gemfibrozil		
Type of HLP	*Parameter*	*Before*	*4 weeks*	*12 weeks*	*24 weeks*
IIa	*n*	5	3	5	4
	$\bar{x}$	1.53	1.18	1.15	1.05
	SEM	0.21	0.56	0.30	0.24
	Δ%		−23	−25	−31
IIb	*n*	3	3	3	—
	$\bar{x}$	2.69	2.64	1.81	—
	SEM	0.17	0.62	0.39	—
	Δ%		−2	−33	
III	*n*	3	3	3	3
	$\bar{x}$	2.90	1.77	1.46	2.00
	SEM	0.45	0.50	0.28	0.18
	Δ%		−39	−50	−31
IV	*n*	15	15	15	14
	$\bar{x}$	3.30	2.05■	2.00■	2.21●
	SEM	0.26	0.22	0.26	0.28
	Δ%		−38	−39	−33

Table 2

Plasma cholesterol concentrations (mmol/l) in different types of HLP before and during treatment with gemfibrozil (400 mg twice daily)

			Gemfibrozil		
Type of HLP	*Parameter*	*Before*	*4 weeks*	*12 weeks*	*24 weeks*
IIa	*n*	5	3	5	4
	$\bar{x}$	336	289	271	263●
	SEM	10	19	16	22
	Δ%		−14	−19	−22
IIb	*n*	3	3	3	—
	$\bar{x}$	352	297	259●	—
	SEM	23	30	20	—
	Δ%		−16	−26	—
III	*n*	3	3	3	3
	$\bar{x}$	282	261	253	239
	SEM	40	13	11	7
	Δ%		−7	−10	−15
IV	*n*	15	15	15	14
	$\bar{x}$	253	227■	217■	221■
	SEM	9	9	9	8
	Δ%		−10	−14	−13

Table 3

Plasma VLDL TG concentrations (mmol/l) in different types of HLP before and during treatment with gemfibrozil (400 mg twice daily)

			Gemfibrozil		
Type of HLP	*Parameter*	*Before*	*4 weeks*	*12 weeks*	*24 weeks*
IIa	*n*	5	3	5	4
	$\bar{x}$	0.65	0.53	0.46	0.46
	SEM	0.15	0.38	0.19	0.17
	Δ%		−18	−29	−29
IIb	*n*	3	3	3	—
	$\bar{x}$	1.78	1.69	1.09	—
	SEM	0.12	0.40	0.25	—
	Δ%		−5	−39	—
III	*n*	3	3	3	3
	$\bar{x}$	1.85	1.05	0.79	1.31
	SEM	0.41	0.43	0.22	0.20
	Δ%		−43	−57	−29
IV	*n*	15	15	15	14
	$\bar{x}$	2.33	1.27■	1.31■	1.53●
	SEM	0.25	0.19	0.23	0.28
	Δ%		−45	−44	−34

Table 4

Plasma LDL TG concentrations (mmol/l) in different types of HLP before and during treatment with gemfibrozil (400 mg twice daily)

			Gemfibrozil		
Type of HLP	*Parameter*	*Before*	*4 weeks*	*12 weeks*	*24 weeks*
IIa	*n*	5	3	5	4
	$\bar{x}$	0.56	0.41	0.43	0.42
	SEM	0.07	0.09	0.06	0.02
	Δ%		−27	−23	−25
IIb	*n*	3	3	3	—
	$\bar{x}$	0.79	0.66	0.50●	—
	SEM	0.13	0.13	0.09	—
	Δ%		−16	−37	
III	*n*	3	3	3	2
	$\bar{x}$	0.71	0.48	0.44●	0.49▲
	SEM	0.04	0.08	0.05	0.03
	Δ%		−32	−38	−31
IV	*n*	15	15	15	14
	$\bar{x}$	0.60	0.53	0.47●	0.49
	SEM	0.06	0.03	0.03	0.03
	Δ%		−12	−22	−18

● significant difference on 5% level ■ significant difference on 1% level ▲ significant difference on 0.1% level
n, number of observations $\bar{x}$, mean value SEM, standard error of the mean
Δ%, percentage difference in concentration before and during treatment

The decrease in serum total TG reflected decreases in the TG content of all lipoprotein classes, i.e. very low density (VLDL); low density (LDL) and high density (HDL) lipoprotein fractions (Tables 3 and 4). For VLDL the most pronounced decreases were found in conditions with VLDL elevation (types IIb, III and IV). A significant correlation existed between the initial VLDL concentration of TG and the change in TG content of VLDL (Fig 1) and is expressed by the equation:

$$\Delta\text{VLDL TG concentration (mmol/l)} = -0.80 \times \text{initial VLDL TG concentration (mmol/l)} + 0.68$$

(Calculated from the difference between initial and 12 week concentrations.) The effect on LDL TG was particularly marked in type III HLP.

The decrease in serum cholesterol was the net result of mean decreases in VLDL, decreases or increases in LDL and slight increases in HDL cholesterol concentrations (Tables 5–7). The effect of gemfibrozil on VLDL cholesterol was essentially similar to that on VLDL TG, except in type III in which the VLDL cholesterol decrease was very pronounced. Thus, the initially elevated mean ratio of VLDL to TG in type III was normalized.

For LDL cholesterol a relationship existed

Table 5

Plasma VLDL cholesterol concentrations (mg/100 ml) in different types of HLP before and during treatment with gemfibrozil (400 mg twice daily)

			Gemfibrozil		
Type of HLP	*Parameter*	*Before*	*4 weeks*	*12 weeks*	*24weeks*
IIa	*n*	5	3	5	4
	$\bar{x}$	23	13	17	15
	SEM	4	8	7	3
	Δ%		−43	−26	−35
IIb	*n*	3	3	3	—
	$\bar{x}$	53	41	30	—
	SEM	6	11	6	—
	Δ%		−23	−43	
III	*n*	3	3	3	3
	$\bar{x}$	56	28	19	27
	SEM	13	7	3	3
	Δ%		−50	−66	−48
IV	*n*	15	15	15	15
	$\bar{x}$	49	29	29	31
	SEM	5	4	3	4
	Δ%		−41	−41	−37

Table 6

Plasma LDL cholesterol concentrations (mmol/l) in different types of HLP before and during treatment with gemfibrozil (400 mg twice daily)

			Gemfibrozil		
Type of HLP	*Parameter*	*Before*	*4 weeks*	*12 weeks*	*24 weeks*
IIa	*n*	5	3	5	4
	$\bar{x}$	237	200	179	180●
	SEM	6	24	19	20
	Δ%		−19	−24	−24
IIb	*n*	3	3	3	—
	$\bar{x}$	258	211	186	—
	SEM	19	17	19	—
	Δ%		−18	−28	—
III	*n*	3	3	3	3
	$\bar{x}$	178	177	182	158
	SEM	32	11	5	7
	Δ%		−1	+2	−12
IV	*n*	15	15	15	14
	$\bar{x}$	159	153●	146	149
	SEM	8	10	9	10
	Δ%		−4	−8	−6

Table 7

Plasma HDL cholesterol concentrations (mmol/l) in different types of HLP before and during treatment with gemfibrozil (400 mg twice daily)

			Gemfibrozil		
Type of HLP	*Parameter*	*Before*	*4 weeks*	*12 weeks*	*24 weeks*
IIa	*n*	5	3	5	4
	$\bar{x}$	63	72	65	66
	SEM	10	13	9	12
	Δ%		+16	+3	+5
IIb	*n*	3	3	3	—
	$\bar{x}$	45	41	44	—
	SEM	6	2	4	—
	Δ%		−9	−2	—
III	*n*	3	3	3	3
	$\bar{x}$	44	49	46	43
	SEM	8	10	9	4
	Δ%		+11	+5	−2
IV	*n*	15	15	15	14
	$\bar{x}$	38	43●	42	42
	SEM	2	3	2	3
	Δ%		+13	+11	+11

● significant difference on 5% level
■ significant difference on 1% level
n, number of observations
$\bar{x}$, mean value
SEM, standard error of the mean
Δ%, percentage difference in concentration before and during treatment

between initial LDL cholesterol and the effect of treatment which is given by the equation:

ΔLDL cholesterol (mg/100 ml)= $-0.45 \times$ initial LDL cholesterol (mg/100 ml) + 61 (Fig 2).

Therefore the greatest decreases of LDL cholesterol were achieved in type IIa and type IIb HLP, while increases were often seen in type IV HLP where LDL cholesterol was initially low.

Maximum effect was achieved for VLDL TG and cholesterol after four weeks on the drug. LDL cholesterol and TG continued to decrease for 12 weeks. In type IV the HDL cholesterol increase was already noted after four weeks and then remained constant, while the maximum decrease in HDL TG was not reached until after 12 weeks. Thereafter lipoprotein concentrations mainly remained constant throughout the study.

Discussion

This study demonstrated that gemfibrozil is a well-tolerated drug with few side effects, even after treatment for several months. It lowers VLDL, LDL and HDL TG concentrations, the effect on VLDL TG being dependent on the initial lipoprotein concentrations. In addition, the initial LDL cholesterol concentration determined the decrease of that lipoprotein lipid by the drug.

In this study no comparison has been made on a controlled basis with other lipid lowering drugs.

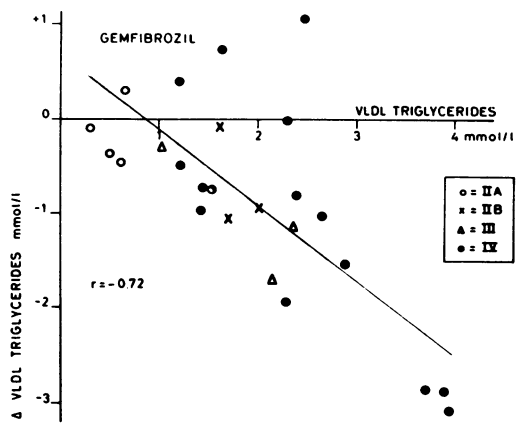

Fig 1 *Relation between the changes in VLDL (ΔVLDL) TG concentration (mmol/l) induced by gemfibrozil and the pretreatment level of VLDL*

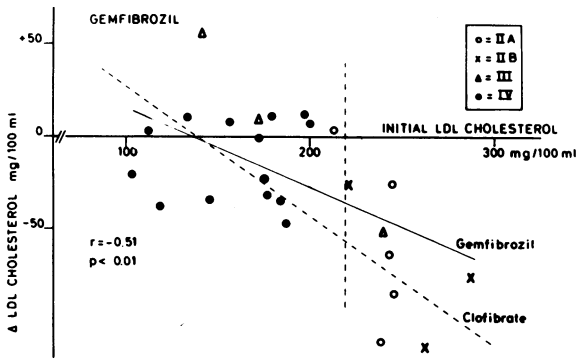

Fig 2 *Relation between the changes in LDL (ΔLDL) cholesterol concentration (mg/100 ml) induced by gemfibrozil and the pretreatment level of LDL cholesterol*

However, the relationship between the initial LDL cholesterol concentration and the change in concentration caused by the drug is very closely related to that of clofibrate reported by Carlson *et al.* (1974) and given by the equation:

$$\Delta\text{LDL cholesterol} = 0.70 \times \text{LDL cholesterol} + 97$$

Thus the equation for gemfibrozil predicts that when pretreatment LDL cholesterol is below 135 mg/100 ml, the LDL cholesterol effect will be positive, i.e. LDL cholesterol will increase. When LDL cholesterol is above this value the treatment will result in a negative effect, i.e. in a lowering of LDL cholesterol. The corresponding figure for clofibrate, according to the equation, is 138 mg/100 ml. Thus from this viewpoint the effects of gemfibrozil and those of clofibrate seem very similar.

The increase in HDL cholesterol concentrations noted in type IV HLP could be regarded as a beneficial effect in view of current concepts of lipoprotein metabolism in which HDL has been given a protective role in the accumulation of lipid in the arterial wall. However, the increase was no greater than could be expected from the known negative relationship between VLDL TG and HDL cholesterol (Olsson & Carlson 1975*b*).

In the present study the intermediate density lipoprotein (IDL) (d = 1.006–1.019) was not isolated. However, the pronounced effect of the drug on LDL TG and also on VLDL cholesterol, especially in type III HLP, indicates that gemfibrozil is particularly efficient in reducing IDL levels.

Summary

The lipoprotein lowering effect of gemfibrozil, 400 mg twice daily, was studied for 24 weeks in 26 subjects with primary hyperlipoproteinæmia (type IIa, 5; IIb, 3; III, 3; and IV, 15). Maximum effects were noted after four weeks on very low density lipoproteins (VLDL) and after 12 weeks on low density lipoproteins (LDL), these effects remaining throughout the study. Gemfibrozil decreased VLDL triglycerides (TG) in all types of hyperlipoproteinæmia according to the equation:

$$\Delta\text{VLDL TG (mmol/l)} = -0.80 \times \text{initial VLDL TG concentration} + 0.68$$

The drug affected the low density lipoprotein (LDL) cholesterol according to the equation:

$$\Delta\text{LDL cholesterol} = -0.45 \times \text{initial LDL cholesterol} + 61$$

This means that LDL cholesterol on average decreased if the initial LDL concentration was above 135 mg/100 ml and increased below that concentration. LDL TG and high density lipoprotein (HDL) TG concentrations also decreased significantly. A slight increase in HDL cholesterol concentration occurred after administration of gemfibrozil. Two subjects had to stop treatment because of nausea and abdominal pain respectively, attributed to the drug. No biochemical side effects were noted.

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