Trial of Once Daily Gemfibrozil (900 mg) in the Treatment of Hyperlipidemia in Diabetes

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Gemfibrozil is a lipid regulator with proven efficacy in dyslipidemia. In an extensive long term study, the Helsinki Heart Study, Gemfibrozil 600 mg produced a significant reduction in total triglyceride and a significant increase in high density lipoprotein cholesterol.

Introduction

Lipid abnormalities are a common sequalae of the metabolic aberrations in diabetes. Hyperlipidemias secondary to diabetes are sometimes corrected with improved metabolic status. However, specific treatment with lipid lowering agents become necessary in primary forms of hyperlipidemias where the increase is due to abnormalities in the synthesis and/or degradation of lipids and in other cases where the lipid levels are persistently raised. Gemfibrozil is a lipid regulator with proven efficacy in dyslipidemia. In an extensive long term study, the Helsinki Heart Study, Gemfibrozil 600 mg produced a significant reduction in total triglyceride and a significant increase in high density lipoprotein cholesterol[1]. Over the five year study period, there was a 34% reduction in the overall incidence of coronary heart disease (CHD) in Gemfibrozil treated group.

This study reports on a trial of Gemfibrozil 900 mg given once a day in diabetic patients with hyperlipidemia.

Materials and methods

Patients

Non Insulin Dependent Diabetes Mellitus (NIDDM) patients with hyperlipidemia, either Type II B (or) Type IV according to the Fredrickson classification were selected from those attending the M.V. Diabetes Specialities Centre at Chennai. Informed consent of the patients was obtained for the trial. Patient of both sexes and aged above 18 years were included in the study. The selection criteria were:

1. Hyperlipidemia type IIa, IIb and IV with atleast the following plasma levels at the end of 4 weeks washout period.

   Total cholesterol > 240 mg/dl

   and/or

   Total triglycerides > 175 mg/dl
2. Controlled NIDDM patients.
3. Patients were not using any lipid lowering agents.
4. None had liver, kidney (or) gall-bladder disease.
5. Cardiovascular disease such as unstable or variant angina, valvular disease, arrhythmias or a history of myocardial infarction was excluded.
6. Any medication affecting blood lipid levels such as : beta blockers, exchange resin, thyroid hormones, male and female hormones—including oral contraceptives, insulin, nicotinic acid, corticosteroids, thiazide or other diuretics, salicylates, or MAO inhibitors was excluded.

Study design

The study was conducted on 20 NIDDM patients, 11 male and 9 female with a mean age of 52 ± 11 years. 14 patients had type II hyperlipidemia and 6 had type IV hyperlipidemia. Patients were started on Gemfibrozil (900 mg) one daily after an initial run-in-period of one month and the period of the

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trial was 8 weeks.

All patients were given a high carbohydrate high fibre (HCHF) diet[3]. The diet was kept constant throughout the study. Adherence to the diet was checked by a dietician at each visit. A bottle containing 30 tablets were given and during the monthly review patients were asked to bring the left over tablets to ensure that the tablets were taken regularly. Antidiabetic treatment was continued as usual.

Clinical investigations

Patient's clinical history was recorded at the first visit. At each visit, the weight, blood pressure and pulse rate were recorded. ECG and ophthalmoscopy were done at the end of wash-out period and at the end of 8 weeks. A complete lipid profile was done at the time of recruitment which included total serum cholesterol, serum triglycerides and HDL cholesterol estimations. LDL cholesterol was calculated using Freidewald formula. At entry into the study and at 8 weeks, the lipid profile was measured again. Fasting and post-prandial plasma glucose, haematology, blood urea and serum creatinine, serum bilirubin, SGOT, SGPT, serum creatinine, alkaline phosphatase, uric acid and creatine phosphokinase were estimated at the end of washout period and at the end of treatment.

All biochemical studies were done by Cornign Express Plus Auto Analyser (Cornign U.S.A.) using kits supplied by Boehringer Mannheim, Germany.

Statistical analysis

All values are expressed as Mean + Standard Error of Means (SEM). P value < than 0.05 was considered significant. Paired T test was done to look for differences between means. A change of 10% or more was considered as satisfactory response.

Results

Table 1 shows the result of the physical examination. Table 2 gives the baseline characteristics of the study patients. Of the 23 patients, who entered the trial, there were 3 drop outs. Out of the remaining 20 patients who completed the trial, 8 had hypertension and 2 had ischaemic heart disease, 2 patients had family history of hyperlipidemia and 6 had arcus senilis but none of the patients had xanthomata.

One patient developed allergic rash which was possibly related to the drug but was not excluded from the study. None of the routine biochemical parameters showed statistically significant differences between pre and post-treatment mean levels, but one patient's CP kinase increased from 82 IU/l to 253 IU/l after taking the drug.

Table - 1 **Physical examination at follow-up visits**

Characteristics	At Recruitment	At Entry	At the end of 4 weeks	At the end of 8 weeks
Weight (kg.)	65.3±2.0	65.6±2.0	65.5±2.2	65.6±2.2
Pulse rate/min	78±3	80±3	79±2	76±2
Blood pressure Systolic (mmHg)	136±4	138±3	133±3	134±2
Diastolic(mmHg)	83±1	83±2	80±2	84±2

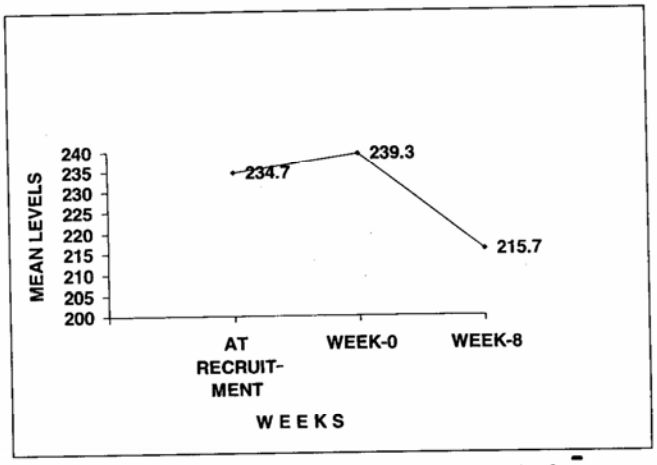

Figure 1 : Change in mean cholesterol after Gemfibrozil (900 mg)

Table - 2 **Efficacy and tolerance lopid (gemfibrozil 900 mg) in hyperlipidem**

No. of Evaluable patients		20
Sex	Male Females	11 9
Age (Years)	Mean + SEM	52.1±2.5
Diet	Strictly veg. Mostly veg. Mostly Non-veg.	7 (35%) 12 (60%) 1 (5%)
Occupation	Manual Semi - Manual Sedentary	Nil (0%) 12 (60%) 8 (40%)
Smoking	Yes No	Nil (0%) 20 (100%)
Alcohol	Yes No	Nil (0%) 20 (100%)

Table - 3 Results of the lipid parameters before and after gemfibrozil

Variable	Pre-treatment	Post-treatment	P Value
Total cholesterol	239±10	216±7	N.S.
Total triglyceride	391±87	177±10	P=0.05
LDL cholesterol	142±8	141±6	N.S.
HDL cholesterol	33±2	36±1.6	N.S.
Total Chol/HDL Ratio	7.73±0.7	6.26±0.3	N.S.
* Significant at P < 0.05	All values are mg/dl		

Table 3 shows the results of the lipid parameters before and after Gemfibrozil (900 mgm) treatment. It can be seen that there was a slight reduction in total cholesterol whereas there was a marked reduction in triglyceride level from 390 to 176 mg% which was statistically significant. There was no significant change in the LDL or HDL cholesterol. There was however a significant reduction in the total cholesterol/HDL ratio.

Table 4 shows the percentage change and percentage of patients showing satisfactory responses after Gemfibrozil (900mg) treatment.

Individual Analysis of Lipoprotein Levels

Effect on cholesterol

It can be seen that there was a slight reduction in cholesterol. Decrease in 10% and above was found in 8 patients (40%), decrease between 0% -10% was found in 6 patients (30%) and in 6 patients (30%) there was a slight increase in cholesterol levels.

Effect on triglycerides

Table - 4 Effect of treatment on lipoproteins

Lipoproteins	Mean percentage change	Percentage of patients showing satisfactory response
Total cholesterol	(↓) 7.3	40%
Total triglyceride	(↓) 42.9	95%
LDL cholesterol	(↓) 4.9	18%
HDL cholesterol	(↑) 10.5	45%
Total Chol/HDL ratio	(↓) 12.5	55%
LDL/HDL ratio	(↓) 1.2	41%
(↑) Rise	(↓) Decrease	

There was a marked reduction in all patients with a decrease in mean triglyceride level from 390 to 176 mg% which was statistically significant. There was a decrease of 10% and above in 19 patients (95%) and a 0% to 10% decrease was noted in one patient (5%).

Effect on LDL cholesterol

There was decrease of 10% and above in 3 patients (18%) and a decrease of 0-10% was found in 7 patients (41%) and 7 patients (41%) showed rise in LDL levels.

Effect on HDL cholesterol

Decrease of 10% and above was found in 9 patients (45%) and 0%-10% was found in 7 patients (35%) while a fall in HDL was found in 4 patients (20%).

Effect on ratio of total to HDL cholesterol

Satisfactory response was found in 11 patients (55%), 0%-10% decrease was found in 4 patients (20%) and a rise is found in 5 patients (25%). Figures 1-5 summarize the response of Gemfibrozil 900 in graphical form.

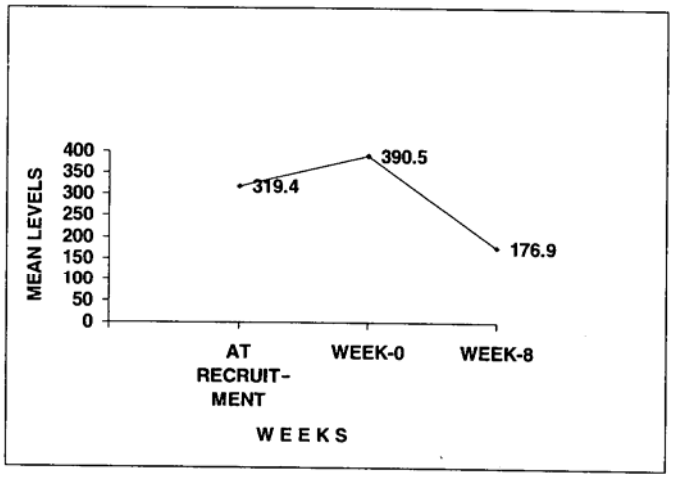

Figure 2 : Change in mean triglycerides after Gemfibrozil 900

Discussion

This study reports on the effect on Gemfibrozil (900 mg) in patients with hyperlipidemia. There was a significant reduction in triglyceride levels in all patients and the HDL level increased in 45% of patients. Thus, Gemfibrozil (900 mg) is an effective drug in diabetic patients with severe hypertriglyceridemia[4]. It is also useful in patients with mixed hyperlipidemia although there is little effect on LDL cholesterol levels.[5,6]

Gemfibrozil (900 mg) given once daily for 2 months did not produce any adverse effects on glucose metabolism in non insulin dependent diabetic. However more studies involving longer periods of treatment are required to determine effects of the drug on glucose metabo-

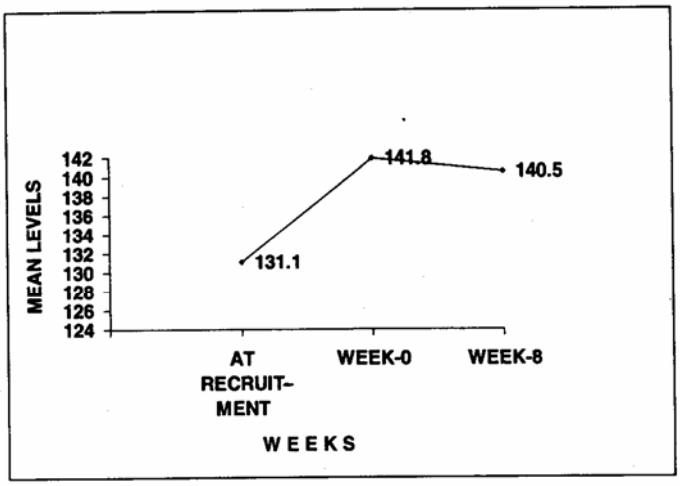

Figure 3 : Change in mean LDL cholesterol after Gemfibrozil (900 mg)

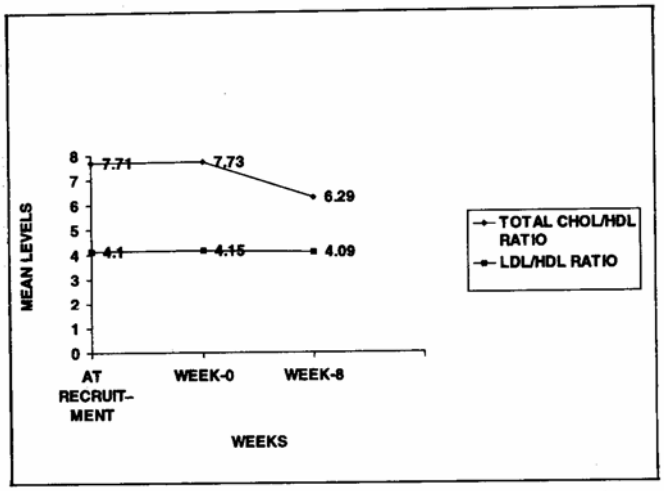

Figure 5 : Change in Total/HDL cholesterol and LDL/HDL cholesterol Ratios after Gemfibrozil 900.

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Gemfibrozil (900 mg) did not have any significant side effects. The drug was easily tolerated by all patients. Skin rash was seen in one patient, but a definite cause-effect relationship could not be established. The cardiac status of all the patients remained normal.

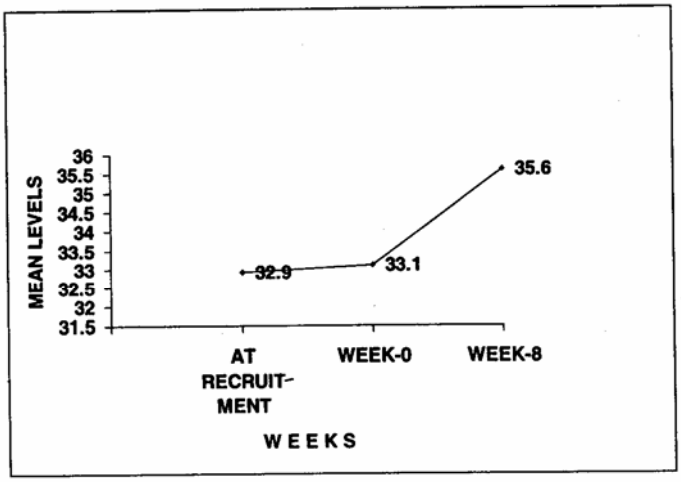

Figure 4 : Change in mean HDL cholesterol after Gemfibrozil (900 mg)

Conclusion

In conclusion Gemfibrozil (900 mg) is a convenient once daily therapy for treatment of hyperlipidemia particularly hypertriglyceridemia which is one of the characteristic lipid abnormalities among diabetic subjects.

References

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