Treatment of Dyslipidemia with Gemfibrozil: A Pilot Study in Pakistan

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SUMMARY:

A series of 65 consecutive male patients were referred and evaluated for hyperlipidemia defined as total fasting serum cholesterol > 270 mg% and/or fasting serum Triglycerides > 200 mg%. Of this referred group, a total of 26 patients fulfilling the study criteria were randomized to Drug Group A (16 patients) and Placebo Group B (10 patients). 8 of the 16 patients in Group A and 8 of the 10 patients in Group B completed the entire 8 weeks protocol. Analysis of the data in the subjects completing the protocol showed a 28% reduction in total Cholesterol in Group A vs. a 5% increase in Group B; a 47% reduction in Triglycerides in Group A vs. a 10% increase in Group B; a 25% reduction in LDL-Cholesterol in Group A vs. a 10% increase in Group B; a 13% increase in HDL-Cholesterol in Group A vs. a 7% increase in Group B and finally a 42% increase in HDL-Chol to Total Chol ratio in Group A vs. 0% (no) change in Group B. In conclusion, Gemfibrozil significantly ($p < 0.05$) lowered Total Cholesterol, LDL-Cholesterol and Triglycerides and raised HDL-Cholesterol and improved the HDLC/TC Ratio in this Pakistani population. The side effects were minor and resulted in 4 of 16 patients (25%) in Group A vs. 2 of 10 (20%) in Group B discontinuing treatment (difference not significant).

Hyperlipidemia, or more appropriately dyslipidemia has been proven to be a major risk factor in the genesis of coronary atherosclerosis (1,2). More excitingly, recents trials have for the first time shown that improvement in the dyslipidemic state reduces that risk of the complications of atherosclerosis (3,4). Also, some degree of regression of atheromatous plaques (5,6) has been documented. In the past, drug treatment of dyslipidemia, not responding to non-pharmacologic measures, has been marred by high side effect profile and poor tolerability of lipid normalizing drugs (7,8,9). With availability of the newer generation of effective and safe lipid normalizing drugs, this situation is fast changing (3,4). In the data reported herein we document the effectiveness and short-term safety and tolerability of the recently introduced agent Gemfibrozil in a randomized, double-blinded, placebo controlled pilot study in Pakistani subjects referred to the National Institute of Cardiovascular Diseases (NICVD), Karachi.

Material and Methods:

Cases were selected from patients referred to the Investigator from the Outpatient Department of the NICVD Karachi during the study period. These patients had a lipid profile done and found to have dyslipidemia. They had all been given

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general instruction to reduce their fat, especially animal fat, intake, discontinue smoking, reduce weight, if over-weight, and, to increase physical activity if sedentary. Both patients with Ischemic Heart Disease and those with isolated Dyslipidemia were included.

Screening and Exclusion Criteria:

All patients had a repeat 12-14 hours fasting lipid profile done alongwith a complete biochemical profile, blood picture and Urine DR. Those with a total Cholesterol > 270 mg% and/or Triglycerides > 200mg% were included in the study if no exclusion criteria existed.

Only males were included due to local conditions and problem of followup in female patients. Age limits kept were 18-65 years. Cases of secondary dyslipidemia such as diabetes mellitus, hypothyroidism, liver cirrhosis, nephrotic syndrome etc. were excluded. Those on anticoagulants or any lipid altering medication within the previous 8 weeks were excluded.

Laboratory Investigations:

At the initial screeing visit and the last visit (after 8 weeks treatment) a detailed history, complete physical examination, complete blood picture and ESR, Urine DR, complete blood chemistry including a 12 to 14 hours fasting total Cholesterol, HDL-Cholesterol, LDL-Cholesterol and Triglycerides as well as a 2 hours post-prandial blood sugar and non-fasting lipids, resting ECG and a X-Ray chest PA view were obtained. During the course of the study, 12 to 14 hours fasting lipids were obtained at 4 weeks after start of treatment.

The total cholesterol was measured directly in the serum. The triglycerides and HDL-cholesterol were measured by enzymatic methods using commercially available standardized kits. LDL-cholesterol was determined by the formula LDL-C = Total C minus HDL – C minus (Trig÷5). LDL-Cholesterol was not calculated if S. Triglycerides were > 700 mg%. Quality control in the laboratory was strictly enforced with coefficent of variation = < 5%.

Treatment Protocol:

After informed consent, subjects were randomly assigned to receive either gemfibrozil or placebo in matching capsules. At weekly visits, patient was enquired as to occurrence of any complaints or problems and compliance was assessed by capsule count. Every effort was made to maintain the double blindness. The randomization codes were kept sealed and unavailable to all involved in patient contact untill all patients had completed the study.

Statistical Methods:

All values are expressed as mean with a single standard deviation. Chi Square analysis and Student T test are used for group comparison. Statistically significant means a p value < 0.05.

RESULTS

Of the subject referred to the Investigator, there were 65 male subjects who did not have any exclusion criteria. On re-testing the lipid profile of these 65, 26 subjects were found to have fasting total cholesterol > 270 mg% and/or Triglycerides > 200mg%. 16 of these 26 subjects were randomized to 8 weeks of drug treatment and 10 subjects to placebo treatment. 8 subjects in the drug treatment group and 8 subjects in the placebo treatment group completed the entire protocol.

Characteristics of the Treatment Groups:

The age, baseline weight at inclusion into the study, weight at completion of the study, associated illness if any, medications if any, in the Gemfibrozil and Placebo groups is given in Table I.

As can be seen, the success of random assignment was reasonably well assured despite the small size of the group and no significant differences were detected.

Lipid Values:

The baseline values represent values after a second screen, the first one having being done

Table 1

Clinical Characterstics of the Two Groups

Group	No	Age (YRS)	WTs (Kg)	WTe (Kg)	Other Dg.	Other Medications	Arcus	Xanthomata
A. Drug	8	46.8 ±13.3	70.9 ±8.2	69.8 ±8.0	HBP – 4 IHD – 3 None – 3	Vasodilators – 5 None – 3	2	0
B. Placebo	8	45.1 ±8.8	61.4 ±8.5	61.9 ±8.8	HBP – 3 IHD – 4 None – 3	Vasodilators – 5 None – 3	5	3

prior to referral. As some general dietary counselling had been given to all subjects prior to referral, a randomly drawn placebo control group was essential to rule out the on-going effect of non-pharmacologic measures in these small but reasonably well matched groups.

There was a significant reduction of total Cholesterol, LDL-Cholesterol and Triglycerides and an elevation of HLD-Cholesterol and the HDL-Cholesterol to total Cholesterol ratio in the Gemfibrozil treated group compared to non-significant changes in these values in the placebo control group. The results are given in Table II and Figure 1. Figure 2 compares the degree of change in those with less severe dyslipidemia versus those with more severe elevation of Cholesterol and Triglycerides. It can be seen that the severe the dyslipidemia, the greater

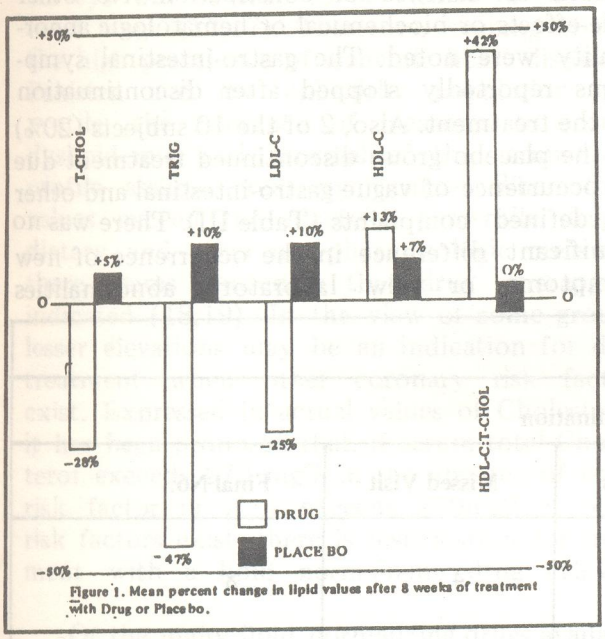

Figure 1. Mean percent change in lipid values after 8 weeks of treatment with Drug or Placebo.

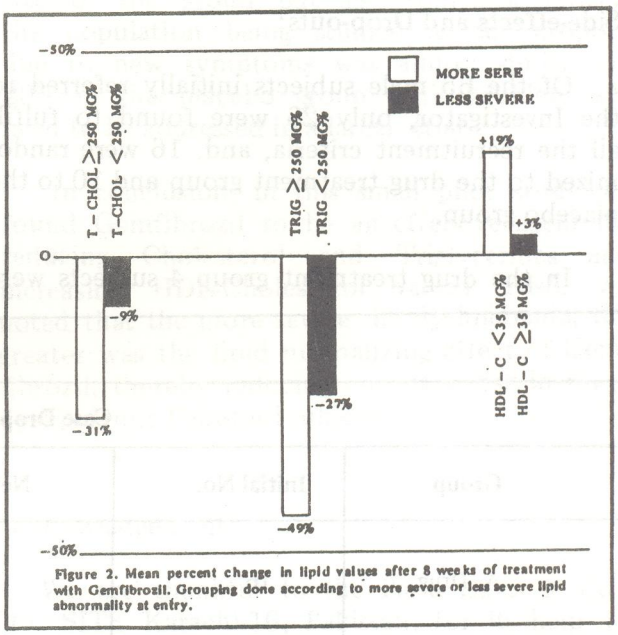

Figure 2. Mean percent change in lipid values after 8 weeks of treatment with Gemfibrozil. Grouping done according to more severe or less severe lipid abnormality at entry.

Table II

Effect of The Two Treatments On Serum Lipids

Parameter		Gemfibrozil	%Change	Placebo	%Change
CHOL MG%	Baseline	283		249	
	Post -Th	203	–28%	261	+5%
TRIG MG%	Baseline	390		245	
	Post–Th	207	–47%	216	+10%
LDL–C MG %	Baseline	171		166	
	Post–Th	129	–25%	182	+10%
HDL–C MG%	Baseline	031		028	
	Post–Th	035	+13%	030	+7%
HDL–C ÷ CHOL RATIO	Baseline	0.12		0.11	
	Post–Th	0.17	+42%	0.11	0%

is the lipid normalizing effect of Gemfibrozil.

The lipid normalizing effects of Gemfibrozil were therefore very significant and additive to any changes that may have occurred due to non-pharmacologic measures.

Side-effects and Drop-outs:

Of the 65 male subjects initially referred to the Investigator, only 26 were found to fulfill all the recruitment criteria, and, 16 were randomized to the drug treatment group and 10 to the placebo group.

In the drug treatment group 4 subjects were excluded due to non-compliance and irregular visits. Another 4 out of this group of 16 (25%) were excluded because of discontinuing treatment due to occurrence of new complaints thought to be drug side-effects. All 4 had complaints of gastro-intestianl upsets with nausea or diarrhea or constipation. No other side-effects or biochemical or hematologic abnormality were noted. The gastro-intestinal symptoms reportedly stopped after discontinuation of the treatment. Also, 2 of the 10 subjects (20%) in the placebo group discontinued treatment due to occurrence of vague gastro-intestinal and other ill defined complaints (Table III). There was no significant difference in the occurrence of new symptoms or new laboratory abnormalities

Table III

Case Drop–outs / Termination

Group	Initial No.	New Symptoms	Missed Visit	Final No.
A. Drug	16	4 (G.I.)	4	8
B. Placebo	10	2 (G.I.)	0	8

between the drug treated versus placebo treated groups.

DISCUSION

In the last few years a significant change has occurred in our thinking as to the definition of what constitutes a 'normal' lipid profile and presently it is generally stated that the ideal total Cholesterol value ought to be below 200mg%, LDL-Cholesterol below 160 mg% and that the HDL-Cholesterol to be 20% or more of the total Cholesterol value (10,11).

The data on lipid values in the Pakistani population is scarce (12). Population samples show a definite unhealthy trend in the last two decades (12, 13). There are small and non-dramatic differences between the 'normals' and patients with clinical ischemic heart disease in various case-control studies (14,15,16). This may well reflect the generally unhealthy serum lipid status of the society which is borne out by the high prevalence of clinical ischemic heart disease in urban and semi-urban Pakistani communities (12).

If one were to accept the above stated ideal lipid levels as true for Pakistan, the mean level of these values in our recent 'normal' population surveys will be seen to be clearly in the non-ideal range (13,17). Therefore, keeping in view the high prevalence of ischemic heart disease in Pakistan and the unhealthy population lipid profile, the relevance of measures to correct dyslipidemia and 'normalize' the serum lipid profile assume great significance. When these values exceed the nineteith percentile despite dietary and other non-pharmacologic measures, there seems consensus that drug therapy is indicated (18,19). In the view of some groups, lesser elevations may be an indication for drug treatment when other coronary risk factors exist. Expressed in actual values of Cholesterol, it has been proposed that, if serum total Cholesterol exceeds 270 mg% in the absence of other risk factor or if it exceeds 250mg% if other risk factors exist, there is justification for treatment with a lipid normalizing drug (19,20).

Of the many lipid normalizing drugs available we chose to study Gemfibrozil due to its free local availability at the time of the trial in addition to its acceptable cost, proven efficacy, low side effect profile and proof that it does indeed reduce cardiovascular morbidity and mortality. The drug Gemfibrozil belongs to the general group of fibric acid derivatives. It is different from clofibrate both in its structure and biologic actions (21,22). The Helsinki Heart Study (4) published in a completed form after start of our study has clearly established the effectiveness of long term treatment of dyslipidemias with Gemfibrozil in a large middle-aged male Finish population.

In view of the existing knowledge, the purpose of this small pilot study was limited to proving efficacy and study side effect profile in our own population to exclude any gross population differences. None was found in the small but tightly controlled groups studied by us, paving the way for a larger more definitive trial when and if thought necessary.

The reductions in total Cholesterol and LDL-Cholesterol and Triglyceride values and the elevations in HDL-Cholesterol and ratio of HDL-Cholesterol to total Cholesterol seen in this study achieved statistical significance and parallel those seen in the Helsinki Heart Study (Fig.1). The side effects seen were minor but did result in a very high dropout rate of quarter of the patients. This may partly be due to the small size of the group but also somehow reflects the population being studied as the dropout due to new symptoms was almost similar i.e. 20% in the placebo group. This problem will need to be addressed in a larger trial.

In conclusion, in this small pilot study we found Gemfibrozil to be an effective agent for reducing Cholesterol and Triglycerides and increasing HDL-Cholesterol values. Also, we noted that the more severe the dyslipidemia, the greater was the lipid normalizing effect of Gemfibrozil, thereby reducing coronary risk in these dyslipidemic Pakistani subjects.

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