Trial of Bezafibrate (Bezalip) in Diabetic Patients with Primary Hypertriglyceridemia

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SUMMARY

A trial of a new hyperlipidemic drug, Bezafibrate, was taken up in diabetic patients with primary hyperlipidemia. The study was done in 25 patients with primary hyperlipidemia. The study was done in 25 patients with type IV and 11 patients with type IIb hyperlipidemia. Blood glucose was controlled prior to the trial with the drug. They took the tablets at a dose of 200 mg t.i.d. after food for 3 months and the lipid parameters were estimated each month. Significant improvement in triglycerides (TG) and cholesterol was seen in both groups of patients ($P < 0.001$).The reduction in TG was seen even within a month and further improvement was observed in the subsequent months. The reduction in serum cholesterol was significant in Type IIb patients. The LDL-cholesterol also decreased in these patients. No significant change was seen in HDL-cholesterol. The drug was well tolerated. The drug is thus found to be safe and effective for treatment of hyperlipidemia, especially hypertriglyceridemia.

INTRODUCTION

Lipid abnormalities are common sequalae of the metabolic aberrations in diabetes. Hyperlipidemias secondary to diabetes are usually corrected with improved metabolic status. However, specific treatment with lipid lowering agents become necessary in primary forms of hyperlipidemias where the increase in due to abnormalities in the synthesis and/or degradation of lipids and not secondary to other disorders and in other cases where the lipid levels are persistently raised. Bezafibrate* is a relatively new drug used in treatment of hyperlipidaemias and is shown to be more effective and well tolerated than the other common drugs used so far[1]. Clinical experience with the drug is limited and restricted only to a few Western countries. Diabetes in Indian patients shows several variations from that reported in Western countries[2]. Hence a trial of the drug was undertaken to study its efficacy and safety in Indian patients with primary forms of hypertriglyceridemia.

MATERIAL AND METHODS

Patients:

Patients with hypertriglyceridemia, either type IIb or IV according to the Fredrickson classification were selected from those attending the Diabetes Research Centre and M.V. Hospital for Diabetes, Madras. Informed consent of the patients was obtained for the trial.

* (2 – [4 – [2 – (4 chlorobenzamido) ethyl] phenoxy] 2 methyl propronic acid

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Patients of both sexes with NIDDM and aged below 70 years were included in the study. The selection criteria were:

1. Patients must be having primary Type IV or Type IIb hyperlipidemia of Fredrickson[3].
   (Serum cholesterol <260 mg/dl and Triglyceride (TG) >200 mg/dl for Type IV
   Serum cholesterol >260 mg/dl and TG >200 mg/dl for IIb)
   These criteria were satisfied by all the patients after a month's treatmet with a calorie-restricted, high carbohydrate, high fibre diet (HCHF diet) and appropriate drug treatment for diabetes[4] (Period 1 to 2).

2. They had significant reduction in plasma glucose (fasting <150 mg/dl and post-prandial <200 mg/dl) at the end of this period (Period 2).

3. Patients were not using any lipid-lowering agents, atleast 8 weeks prior to the start of the study.

4. None had liver, kidney or gall bladder disease.

5. Women with pregnancy or lactation were excluded.

We recruited a total of 142 patients and ıfter the 1st month's trial period with an- diabetic treatment, only 61 patients qualified ır the study, as in the the other 81 the TG ılues decreased below 200 mg/dl. Of these, 5 patients with type IV hyperlipidemia and patients with type IIb were available for the ıree month's study with Bezalip (Boehringher Mannheim, (West Germany).

In the 81 patients, the serum cholesterol and triglyceride values decreased below 260 mg/dl and 200 mg/dl respectively within a month of treatment with the diet and antidiabetic drug therapy. The mean fasting plasma glucose at the start of the study and at the end of the first month were similar to the other two groups having Type IV and Type II hyperlipidemia.

Of the 36 patients qualified for trial with bezafibrate, 25 patients were already known to have hyperlipidemia and had used other hypolipidemic agents prior to the study. The control of hyperglycemia and the use of the calorie restricted low fat diet did not produce satisfactory control of hyperlipidemia. None of them were using the drugs for at least three months prior to this study.

Study Design:

The patients underwent 5 examinations, at monthly intervals marked periods 1 to 5 (Figure 1). During the peirod (1) the patients were on the diet and drug therapy for diabetes only. All patients were given a high carbohydrate high fibre (HCHF) diet with 65% carbohydrate, 20% protein and 15% fat with the total calories ranging from 1400 to 2000 K Cals calcutated accoding to the individual requirements[4]. The diet was kept constant throughout the study. Adherance to the diet was checked by a dietitian at each visit. After the second examination (2nd month) when the plasma glucose was significantly lower, but the cholesterol and TG values were still elevated according to the criteria already mentioned, Bezafibrate (Bezalip) tablets were started. Bezalip was administered at a dose of 200 mg (1 tablet) t.i.d. after food for 12 weeks. Packets containing 100 tablets were given during the monthly review. Patients continued to have the treatment for diabetes. Patients were asked to bring the left over tablets during the reviews,

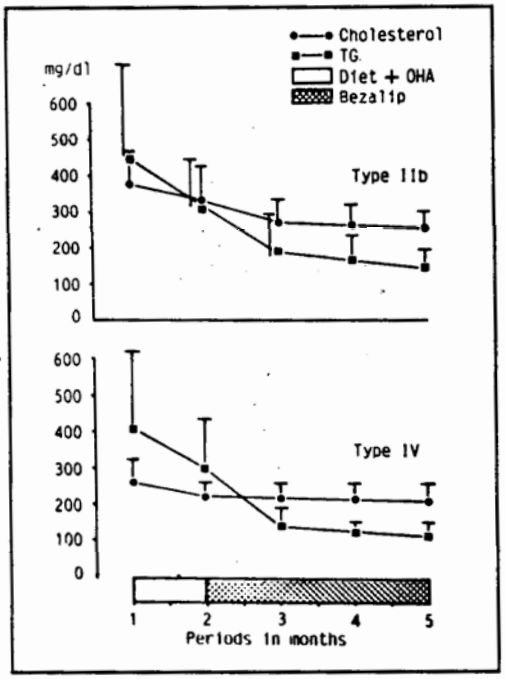

Fig. 1. Changes in serum cholesterol and triglycerides during the trial periods.

TABLE 1.
CHANGES IN THE BIOCHEMICAL PARAMETERS IN PATIENTS WITH HYPERLIPIDEMIA SECONDARY TO DIABETES
(n = 81)

	Initial	After 1 month
Fasting Plasma glucose(mg/dl)	200 ± 88	146 ± 29*
HbAl (%)	10.3 ± 1.6	9.5 ± 0.9*
Cholesterol (mg/dl)	318 ± 92	236 ± 20*
Triglycerides (mg/dl)	426 ± 210	182 ± 40*

Values are mean ± SD
*p <0.001 compared to initial value.

to ensure that the tablets were taken regularly.

Clinical Investigations

Patient's clinical history was recorded at the first visit. At each visit, weight and blood pressure were recorded. Blood samples were drawn after an overnight fasting for fasting plasma glucose (FPG) (Glucose oxidase — Boehringher Mannheim Kit), Glycosylated haemoglobin[5] (HbAl), Serum total cholesterol[6], HDL[7] and LDL[8] Cholesterol, and triglycerides[9]. Serum creatinine, SGOT, SGPT, and alkaline phosphatase[12] estimations were also done using standard colorimetric procedures[10]. Side effects of the drugs, if any, were recorded.

Statistical Analysis

The results are presented in the tables as Mean ± standard deviation. Wilcoxon's signed rank test was used for comparison of the values at time periods 2 and 5, i.e., at the start of Bezalip treatment and after 3 months of treatment.

RESULTS

Hyperlipidemia due to diabetes:

In 81 patients (M:F 51:30), the total cholesterol and triglyceride values decreased below 260 mg/dl and 200 mg/dl respectively, during the first month of the study when they were treated only with the diet and drug therapy for diabetes. Table 1 shows the changes in these parameters in this study group.

Type IV Hyperlipidemia:

Twenty five patients, 13 men and 12 women, with a mean age of 50.7 ± 7.9 years completed the 4 month trial period. Duration of diabetes varied between few months to 12 years with a mean value of 5.3 ± 3.3 years. Twenty patients were on oral antidiabetic drugs, four were treated with insulin and one patient was only on diet therapy. During the study period, there was no significant change in the body weight in these patients. Table 2 shows the mean values of the various biochemical parameters at the beginning and during the follow-up periods.

TABLE 2.
RESULTS IN PATIENTS WITH TYPE IV HYPERLIPIDEMIA (N = 25)

Time periods (months)	(1)	(2)	(3)	(4)	(5)
Fasting Blood Glucose mg/dl	182 ± 49	141 ± 34	126 ± 23	114 ± 27	123 ± 32*
HbA1 %	10.0 ± 1.4	9.4 ± 0.85	9.05 ± 0.69	8.8 ± 0.81	8.7 ± 0.64*
Triglycerides (mg/dl)	404 ± 203	295 ± 138**	138 ± 52	119 ± 33	126 ± 28*
Cholesterol (mg(dl)	256 ± 58	224 ± 24**	210 ± 25	212 ± 26	212 ± 20*
HDL Cholesterol (mg/dl)	155 ± 22	149 ± 24	134 ± 17	140 ± 26	141 ± 20
LDL cholesterol (mg/dl)	155 ± 22	149 ± 24	134 ± 17	140 ± 26	141 ± 20
Creatinine mg/dl	0.71 ± 0.1	0.74 ± 0.08	0.76 ± 0.07	0.75 ± 0.08	0.7 ± 0.16
SGOT IU/l	18 ± 6	19 ± 8	15 ± 7	20 ± 7	18 ± 8
SGPT IU/l	18 ± 9	20 ± 9	13 ± 4	16 ± 6	16 ± 6
Alkaline Phosphatase IU/l	56 ± 17	53 ± 15	47 ± 33	45 ± 16	50 ± 24
Body Wt Kg	64.6 ± 8.2	64.9 ± 8.2	64.5 ± 8.4	65 ± 8.3	65.2 ± 8.5

* $p < 0.001$ compared to (2) ** $p < 0.001$ compared to (1)
Values are mean ± SD

TABLE 3.
RESULTS IN PATIENTS WITH TYPE IIb HYPERLIPOPROTEINEMIA (N = 11)

Time periods (months)	(1)	(2)	(3)	(4)	(5)
Fasting blood Glucose mg/dl	208 ± 94	138 ± 35	119 ± 19	117 ± 19	119 ± 32
HbA1 %	11.3 ± 2.2	9.5 ± 1.2	8.8 ± 0.8	8.6 ± 0.6	8.6 ± 0.6
Cholesterol mg/dl	371 ± 88	323 ± 92	259 ± 61	251 ± 62	243 ± 47*
LDL cholesterol mg/dl	233 ± 46	230 ± 87	179 ± 49	181 ± 48	169 ± 41*
HDL cholesterol mg/dl	50 ± 2	44 ± 8	47 ± 7	48 ± 5	49 ± 4
Triglycerides mg/dl	436 ± 278	306 ± 127	170 ± 105	153 ± 59	140 ± 44*
Creatinine mg/dl	0.73 ± 0.11	0.73 ± 0.09	0.79 ± 0.08	0.73 ± 0.08	0.71 ± 0.06
SGOT IU/l	20 ± 8	18 ± 9	19 ± 9	25 ± 11	19 ± 7
SGPT IU/l	20 ± 8	17 ± 9	15 ± 7	18 ± 6	17 ± 4
Alkaline phosphatase IU/l	51 ± 18	51 ± 15	44 ± 20	44 ± 13	40 ± 3
Body Wt Kg	62 ± 11	63 ± 13	63 ± 13	63 ± 12	61 ± 9

Values are mean ± SD; *$p < 0.001$ compared to (2)

The fasting blood sugar decreased significantly during the placebo period (1st month) and the mean values continued to be lower than 130 mg/dl throughout the study. Glycosylated haemoglobin (HbA1) also showed a reduction in the 1st month (non-significant) and the value decreased more significantly during the subsequent months.

The mean value for TG was 404 ± 203 mg/dl at the start of the study and it decreased to 295 ± 138 mg/dl with control of blood glucose (Time 1 to 2). However, all the values were above 200 mg/dl at period 2. The value decreased significantly ($P < 0.001$ compared to the 1st month (placebo value) even in the first month of treatment with Bezalip. During the second and third months with Bezalip, the values decreased further. The difference in the values between periods 2 and 5 was highly significant ($p < 0.001$).

The mean cholesterol value showed a significant reduction with control of blood glucose (256 ± 58 to 224 ± 24 mg/dl, $P < 0.001$). Further reduction was observed during the subsequent months also. Figure 1 shows the changes in cholesterol and triglyceride concentrations in the type IV patients.

HDL cholesterol value did not show any significant difference during the study. Concentration of LDL cholesterol decreased with Bezalip treatment (Non-significant).

Type IIb hyperlipidemia:

The results in eleven patients with Type IIb hyperlipidemia are shown in Table 3.

Significant reduction was noted in the cholesterol and triglyceride values between periods 2 and 5 ($P < 0.001$ for cholesterol and TG) (Figure 1). LDL-Cholesterol showed a decrease ($P < 0.001$); but the HDL-cholesterol values did not change significantly.

There was no significant change in the body weight in any of these patients during the study period.

Side Effects:

One patient discontinued the drug due to severe gastritis. One patient had urticaria initially, which subsided later. Another patient had oral ulcers and one patient felt weak after taking 3 tablets each day. However, both of them could continue 2 tablets/day without problems. Kidney function tests (blood urea, serum creatinine, urinary albumin quantitative estimations) and liver function tests remained normal throughout the study period in all patients.

DISCUSSION

Results of this trial show that bezalip is highly effective in the treatment of hyperlipidemia, especially hypertriglyceridemia. The reduction in TG values are obtained even within a month in most patients and further improvement is observed in the subsequent two months. In none of the patients, the TG value remained above 150 mg/dl after 3 months of treatment with Bezalip.

Serum cholesterol concentration also decreased significantly with Bezalip, in the patients with Type IIb hyperlipidemia. Another beneficial effect of the drug is that it reduces the LDL-cholesterol concentration, which is considered a risk factor for vascular diseases.

We did not observe any significant increase in the HDL-cholesterol concentration. These observations agree with those of some workers [11,13], but disagrees with few others [14-16] who observed an improvement in the HDL-cholesterol concentration with Bezafibrate treatment. Senderey[11], who also had studied

the effect of the drug in NIDDM patients had stated that the divergent results observed could be due to the different types of patients involved in the study. It has to be stressed that the values were well within normal limits in all the patients in our study.

The reduction in fasting plasma glucose values was significant in the placebo period (period 1 to 2) in all groups of patients, whereas the subsequent changes were not so marked. It is ulikely that the hypolipidemic effect could have been due to the action of the diet and glycemic control only during periods 2 to 5, since such changes were not evident in Type IV and Type II patients during the placebo period when maximum reduction in the plasma glucose was obtained. Addition of Bezafibrate hastens the hypolipidemic changes. There was no significant weight reduction in any group and thus this factor also could not have contributed to the hypolipidemic effect.

In summary, we conclude that Bezafibrate is a safe and effective drug for treatment of hyperlipidemia, especially hypertriglyceridemia.

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