EFFECTS OF CLOFIBRATE IN HYPERLIPIDEMIA: A CONTROLLED TRIAL

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Abstract

In a series of 30 cases of hyperlipidemia, antilipidemic effects of clofibrate were studied in a controlled trial. The mean serum cholesterol level was reduced from 360 mg/100 ml to 270 mg/100 ml ($P < 0.05$) after treatment for 3 months and these results were regarded as satisfactory in 19/25 cases (76%) of hypercholesterolemia. The mean serum triglyceride was reduced from 305 mg/100 ml to 180 mg/100 ml after treatment ($P < 0.05$), and this was considered as satisfactory in 10/16 cases (62%) of hypertriglyceridemia. Two cases (6.5%) complained of weakness and one (3.3%) developed mild gastro-intestinal symptoms but no serious side-effect was recorded.

Introduction

Hyperlipidemia is one of the cardinal risk factors for coronary heart disease. The significance of hyperlipidemia in coronary heart patients in our community is not well established. In Pakistan lower mean serum cholesterol level (200 mg/100 ml, S.D.±50 mg/100 ml) as compared to the European series, have been reported by Syed and co-workers (1973). Clofibrate (Atromid-S) has been reported to be a very effective antilipidemic agent (Green and Margetts, 1967; Oliver, 1968). It has been shown that use of clofibrate resulted in reduction of serum cholesterol and triglyceride with an associated reduction of coronary heart disease (Krasno and Kidera, 1972). Published data from Pakistan on the antilipidemic effects of clofibrate is not available. This paper describes our experience on the use of clofibrate in patients with hyperlipidemia in a controlled trial.

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Material and Methods

Thirty consecutive out-patients, seen in the Muhammadi Hospital, with a serum cholesterol of 300 mg/100 ml or above, and/or serum triglyceride 250 mg/100 ml or above were included in the trial. Serum cholesterol was measured by Lieberman Burchard Photometric Method (Person et al., 1953) and serum triglyceride by Lutidin Photometric Method (Lartillot et al., 1970).

After acceptance in the trial each case was given placebo capsules, identical in shape and colour to Atromid-S, one three times a day for a month. At the end of the placebo period the following estimations were carried out: serum cholesterol, serum triglyceride, serum bilirubin, serum glutamic oxaloacetic transaminase and erythrocyte sedimentation rate.

Clofibrate (Atromid-S, I.C.I.) was then given to each case, 500 mg capsules three times a day, for 3 months. The cases were reviewed fortnightly and serum cholesterol and triglyceride estimations were carried out on each follow-up. In order to monitor possible hepatotoxic effects of Atromid-S, serum bilirubin and serum oxaloacetic transaminase were measured monthly.

These included 30 cases, 22 males and 8 females, age range 33-74 years (mean 49 years); 14 cases (47%) had hypercholesterolemia (serum cholesterol 300 mg/100 ml or above) and 5 cases (17%) had hypertriglyceridemia (serum triglyceride 250 mg/100 ml or above) and II cases (36%) had both hypercholesterolemia and hypertriglyceridemia. Hypercholesterolemia was thus present in 25 out of 30 cases, and hypertriglyceridemia in 16 out of 30 cases.

Diseases associated with hyperlipidemia are shown in Table I.

Table I: Hyperlipidemia: Associated Diseases

Diseases	*Cases*
Coronary Heart Disease	16 (53%)
Diabetes Mellitus	5 (17%)
Nephrotic Syndrome	3 (10%)
Myxoedema	1 (3%)
'Asymptomatic'	5 (17%)

Results

Hypercholesterolemia

In 25 cases with hypercholesterolemia the mean serum cholesterol level was 360 mg/100 ml before treatment which reduced to 270

mg/100 ml after 3 months of treatment; a mean reduction of 90 mg/100 ml ($P \leq 0.05$), (Table II). In terms of individual cases, 19 cases (76%) showed 'satisfactory' result i.e. reduction of serum cholesterol 250 $\leq$ mg/100 ml. However, 6 cases (24%) showed 'unsatisfactory' result i.e. although most of these cases showed some reduction in serum cholesterol but the level remained above 300 mg/100 ml (Table III). One of these cases had a very high serum cholesterol level of over 1,000 mg/100 ml initially, and a reduction to 800 mg/100 ml was obtained after three months of treatment.

Table II: Effects of Clofibrate on Serum Lipids

Serum Lipids (*Cases*)	*MEAN SERUM LEVEL* *Before Treatment* mg/100 ml	*After Treatment* mg/100 ml	*Reduction* mg/100 ml
Cholesterol (25)	360	370	90 ($P \leq 0.05$)
Triglycerides (16)	305	180	125 ($P \leq 0.05$)

Table III Results of Clofibrate in Cases of Hyperlipidemia

Cases	*Satisfactory*	*Unsatisfactory*
Hypercholesterolemia 25	19(76%)	6(24%)
Hypertriglyceridemia 16	10(62%)	6(38%)

Hypertriglyceridemia

In 16 cases with hypertriglyceridemia the mean serum triglycerides level of the group was 305/100 ml before treatment and reduction to a mean level of 180 mg/100 ml was achieved after 3 months of therapy with Atromid-S. The mean reduction of 125 mg/100 ml was significant ($P \leq 0.05$). In terms of individual cases 10 cases (62%) showed satisfactory results i.e., reduction of serum triglyceride $\leq$ 200 mg/100 ml. However, 6 cases (38%) showed 'unsatisfactory' result, and 5 of these cases showed lesser degree of reduction in serum triglyceride level. One case (6%) with marked hyperlipidemia (high cholesterol and triglyceride) showed in serum triglyceride level.

Side Effects

Two cases (6.6%) complained of weakness, one (3.3%) developed transitory diarrhoea and another sickness, but hepatotoxicity was not observed. The liver function tests remained normal in all these cases and only one case (3.3%) showed slight increase in serum glutamic oxaloacetic transaminase (S.G.O.T.). In no patient clofibrate was discontinued because of side-effects.

Discussion

Coronary heart disease has acquired epidemic proportions in the developed countries, and the important risk factors include hypertension, hyperlipidemia, smoking, inactivity, obesity and increased stress and strains of life. In a hospital series of 370 consecutive cases of coronary heart disease we have found hypercholesterolemia in 69% of cases and hypertriglyceridemia in 55% of cases (Ilyas et al., 1975). It has been shown by the Framingham study, over a 12 years follow up, that hypercholesterolemia alone or in combination with other risk factors increased the risk of myocardial infarction (Kannel et al., 1967, 1971).

Clofibrate binds serum albumin to displace thyroxine and its metabolites which decrease hepatic synthesis of cholesterol, triglycerides and glycogen. In addition, transport of free fatty acids is reduced because clofibrate also occupies the binding sites of these acids. Clofibrate has also been reported to decrease platelet adhesiveness (Robinson, 1966; Chakrabarti et al., 1968) and also significantly lowers serum fibrinogen levels (Cotton and Wade, 1969). It is effective in type III, IV and V hyperlipidemia (Levy et al., 1968; Schatz, 1968). When used in conjunction with coumarin derivatives it prolongs anticoagulation (Pavala et al., 1968).

In our series on acceptance in the trial general instructions about decreasing the fat and carbohydrate intake, exercise and weight reduction were given. But in no case serum lipids were lowered substantially and only in those cases in whom the levels were high enough i.e., above the cut-off points mentioned, were included in the study. After treatment with clofibrate the mean level of serum lipids was compared with the pre-treatment level and not with the pre-placebo level. Patients with diabetes mellitus were adequately controlled on oral hypoglycemics prior to starting placebo treatment.

The placebo period of one month in our trial was apparently not very long but this was sufficient to exclude borderline cases of hyperlipidemia in whom persuasion and dietary restriction could lower the serum lipid level significantly. In our series half the cases of hyperlipidemia were associated with coronary heart disease and only in 5 cases (17%) this was not associated with any disease (Table I). In our small series clofibrate lowered serum triglycerides more substantially than serum cholesterol but the reduction was significant for both these serum lipids. In our experience clofibrate used for 3 months significantly and satisfactorily lowered serum cholesterol level in 19/25 cases (76%) and serum triglycerides in 10/16 cases (62%). Except for some weakness or diarrhoea in 3

cases (9%) no serious side effect requiring discontinuation of the drug was observed.

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