ONE YEAR EXPERIENCE WITH PROBUCOL, A NEW HYPOCHOLESTEROLAEMIC AGENT

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SYNOPSIS

A new hypocholesterolaemic agent, Probucol 4,4 (isopropylidenedithio) bis (2.6 d-t-butylphenol) was administered in two daily doses of 500 mgm to ten patients with hyperlipidaemia over a period of twelve months. There was an average reduction in the fasting serum cholesterol of 28.7% compared to the pre-treatment levels (t test $p < 0.001$). There was an average reduction of 18% in the serum triglyceride compared to pre-treatment levels ($p < 0.05$).

Diarrhoea was present in two patients. Two patients developed hyperuricaemia at the end of twelve months' administration of the drug. The drug did not produce any changes in the full bloot count, serum urea, serum electrolytes or liver function tests at the end of the study.

INTRODUCTION

Dietary restriction is the mainstay of treatment of hyperlipidaemia. There is however, still a need for drug treatment in patients who do not respond to dietary restriction. Although there are several drugs available for reducing serum lipids, there is still a need of an effective and safe drug which is well tolerated by patients and free from side-effects. This paper reports the experience of one year administration of Probucol 4,4 (isopropylidenedithio bis (2,6 d-t-butylphenol), a new hypocholesterolaemic agent, in the treatment of patients with hypercholesterolaemia.

MATERIALS AND METHODS

Ten patients with hyperlipidaemia were included in the study. The type of hyperlipidaemia was classified according to Frederichson's method. Children under the age of 16 years and pregnant patients were excluded from the study. Informed consent was obtained from all patients.

There were nine males and one female in the study group. The age of patients ranged from 28 years to 52 years, with a mean age of 39.7 years. Seven patients were Chinese, two were Indians and one was of the Malay ethnic group.

There were four patients with Type IIa hyperlipidaemia, five patients with Type IIb hyperlipidaemia, and one patient with Type IV hyperlipidaemia. Six patients had previous myocardialn infarctions and three patients were managed for angina pectoris.

All patients were on dietary restriction from the time of diagnosis. All patients were on low cholesterol diet and modified low fat diet for a minimum period of six months before the study. The average period of dieting prior to study was 21 months. Patients were selected for inclusion in the study if after the period of dietary control, the fasting serum cholesterol was in the steady state (average of three weekly fasting serum cholesterol) and if the average value exceeded or was equal to 250 mgm/dl. The average of the three stable weekly fasting serum cholesterol was taken as the baseline value. Similar baseline samples were taken for measurment of serum triglyceride levels. Baseline pre-treatment blood samples were taken for full blood counts, serum urea, serum electrolytes, serum uric acid and liver function tests.

No anti-lipidaemic agent was administered for at least three months prior to the study period. The patients were allowed to continue all their other previous medications. Nine patients were on propranolol, three patients were receiving aspirin and one patient was on Wafarin sodium.

The patients were prescribed Probucol 500 mgm twice a day and were seen at monthly intervals. Patients were questioned at each visit for possible side-effects. Physical examination was performed at each visit. Fasting serum cholesterol and triglyceride levels were also measured at each visit.

The patients were instructed to continue with the dietary restriction that they were on.

The serum lipids were estimated after an overnight fast of 12 hours. Serum cholesterol was measured using the Autoanalyzer Method Technicon No SE 40016-FHA. Serum triglyceride was measured using the Autoanalyzer Method Technicon SE 4-00238 SSE.

Full blood count, serum urea, serum electrolytes, serum uric acid and liver function tests were performed before and after the study period.

RESULTS

The mean serum cholesterol level before dietary treatment was 321 mgm/dl, and average serum cholesterol value after dietary treatment was 295.5mgm/dl. There was an average reduction of 8.3%. The mean serum triglyceride value before dietary treatment was 250.5 mgm/dl. This was 267.8 mgm/dl after dietary treatment.

The mean baseline serum cholesterol was 295.5 mgm/dl and mean baseline serum trigylceride level was 267.8 mgm/dl. These were the baseline values taken to assess the reduction in serum lipids after administration of Probucol.

The hypocholesterolaemic effect of Probucol was noticeable after two months of administration of the drug. The mean baseline serum cholesterol value was reduced from 295.5 mgm/dl to a mean of 210.5 mgm/dl at end of twelve months' period of administration of Probucol. The average reduction of serum cholesterol was 28.7% ($p < 0.001$). This is statistically very significant.

The mean baseline serum triglyceride value was 267.8 mgm/dl. The mean serum triglyceride value at end of twelve

TABLE 1: FASTING SERUM CHOLESTEROL LEVELS

Patients	Type of Hyperlipidaemia	Serum Cholesterol Before Diet (mgm/dl)	Baseline Serum Cholesterol (Diet only) (mgm/dl)	Serum Cholesterol at End of 12 Months (Diet + Probucol) (mgm/dl)	Percentage Reduction at End of 12 Months Compared to Baseline (%)
LBH	IIa	360	357	280	—21.6
AA	IIa	350	278	200	—28.1
LTH	IIa	355	367	255	—30.5
NSH	IIa	310	283	200	—29.3
AR	IIb	310	267	225	—15.7
HO	IIb	310	285	190	—33.3
TWC	IIb	290	263	180	—31.6
PR	IIb	330	337	210	—37.7
LY	IIb	330	270	185	—31.5
YYK	IV	265	250	180	—28.0

TABLE 2 : FASTING SERUM TRIGLYCERIDE LEVELS

Patients	Type of Hyperlipidaemia	Serum Triglyceride Before Diet (mgm/dl)	Baseline Serum Triglyceride Diet only (mgm/dl)	Serum Triglyceride at End of 12 Months Diet + Probucol (mgm/dl)	Percentage Reduction at End of 12 Months Compared to Baseline (%)
LBH	IIa	155	80	75	— 6.3
AA	IIa	145	152	110	—27.6
LTH	IIa	150	210	140	—33.3
NSH	IIa	125	123	130	+ 5.7
AR	IIb	360	293	220	—24.9
HO	IIb	290	270	350	+ 29.6
TWC	IIb	310	355	255	—28.2
PR	IIb	240	293	260	—11.3
LY	IIb	240	282	100	—64.5
YKK	IV	490	620	500	—19.4

months was 214 mgm/dl. There was an average reduction of 18% (t test p = 0.022).

The side-effects were minimal. All ten patients tolerated the drug very well. Two patients developed mild diarrhoea from the time of initial administration of Probucol. This subsided after three months in one patient, but persisted in a mild form in the second patient. All ten patients completed twelve months of administration of Probucol.

No changes were found in the full blood counts, serum urea, serum electrolytes and liver function tests at end of twelve months. Two patients developed hyperuricaemia. One patient had an increase of serum uric acid from 5.6 mgm/dl to 9.6 mgm/dl and in another it increased from 7 mgm/dl to 9 mgm/dl. This was probably due to the administration of Probucol. However both patients were asymptomatic.

DISCUSSION

Dietary restriction is the mainstay of treatment in hypercholesterolaemia as most of the drugs have side-effects with long term administration. There is a need for an effective, safe and well tolerated drug for long-term use in those patients who do not respond to dietary measures alone.

Probucol 4,4 (isopropylidenedithio) bis (2,6 — d-t-butylphenol) is a bisphenol with a chemical structure unlike that of other currently available lipid-lowering agents. The hypocholesterolaemic activity of Probucol was discovered in animals by Barnhart and Shea (1).

The use of Probucol in man was reported by Colmore et al (2), Drake et al (3) first and subsequently by others.

Though Probucol has been used in clinical trials for about ten years, the exact mechanism of action is yet to be firmly established. The suggested sites of action are inhibition of lipoprotein formation and/or impaired intestinal mucosal transport of cholesterol (3, 4). Le Lorier et al (4) showed that there was no increase in serum levels of cyclic precursors of cholesterol, indicating that Probucol does not influence the late stages of cholesterol formation. Further studies are needed to elucidate the exact site of action of Probucol.

A significant reduction in serum cholesterol was observed at end of two months of administration of Probucol. At end of twelve months, there was an average reduction of 28.7% in serum cholesterol when compared to the baseline value. These findings are consistent with the results of previous clinical trials using Probucol as the lipid lowering agent (5-13). The average reduction in serum cholesterol was 10 to 15% the range was from 13% to 38%. The study by Le Lorier et al (4) reported a reduction of 13% in serum cholesterol beyond that achieved with a fat-restricted diet alone.

The effect of Probucol at end of six months on serum triglyceride was highly variable. However, there was a significant reduction in serum triglyceride levels at end of twelve months of administration of Probucol. There was an average reduction of 18% compared to the baseline serum triglyceride values. This finding is in contrast to those of other studies which showed no consistent reduction in serum triglyceride after Probucol therapy (4-13).

Diarrhoea was a side effect in two patients in this study. This was mild and was peristent only in one patient. Gastrointestinal symptoms like nausea, diarrhoea, flatulence and abdominal pain were the commonest side-effects in most reports (5).

There were no changes in the serum urea, serum electrolytes, full blood counts or liver function tests. Hyperuricaemia developed in two patients during the course of treatment with Probucol. Hyperuricaemia was reported by Drake et al (3) during therapy with Probucol in females, but not in males. Danowski et al (12) demonstrated no changes in thyroid function, plasma and urinary steroids or glucose tolerance tests in patients treated with 12 to 24 weeks of Probucol. Eosinophilia and rise in creatine phosphokinase (5) have been reported after treatment with Probucol.

Though this study has certain limitations, Probucol appears to be a safe and effective drug in the treatment of patients with hypercholesterolaemia. It has been well tolerated by all the patients and has produced significant reduction in the serum cholesterol and serum triglyceride levels in the patients studied.

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