Colestipol at varying dosage intervals in the treatment of moderate hypercholesterolaemia

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- 1 Bile acid sequestrants such as colestipol are effective lipid lowering agents but have a poor reputation for tolerability particularly when administered at the originally recommended doses. We have investigated a low dosage regimen with varying dosage intervals in order to assess efficacy and tolerability.
- 2 This double-blind, placebo controlled, parallel group study was conducted to investigate the effect of varying administration schedules of colestipol (10 g daily), against placebo in reducing LDL cholesterol levels in patients with moderate hypercholesterolaemia on the American Heart Association step 1 diet.
- 3 Colestipol or matched placebo, was administered as 5 g twice daily (COL am /pm) or 10 g once daily in the morning (COL am) or evening (COL pm) at fixed times with meals.
- 4 All 98 patients who entered the initial 16 week dietary phase, subsequently entered the 12 week active treatment phase and were randomised to placebo or active treatment and to one of the three treatment schedules. Fasting lipid profiles were performed every 4 weeks during both phases.
- 5 All active treatments significantly reduced LDL and total cholesterol compared with placebo (COL am: 17% and 10%, COL pm: 18% and 10%, COL am/pm: 19% and 12% ($P = 0.0001$)). HDL cholesterol rose significantly with COL am (5% ($P = 0.021$)) and COL am/pm (7% ($P = 0.002$)) when compared with placebo while a marginal increase was seen with COL pm (4% ($P = 0.063$)). Colestipol tended to increase serum triglyceride concentrations but the changes were not significant.
- 6 Compliance in all groups was greater than 94%. Significantly fewer patients reported medical events in the COL am group ($P = 0.02$).
- 7 The efficacy and tolerability of colestipol are similar when the drug is given with meals as a single daily dose of 10 g in the morning or evening or as a twice daily dose of 5 g. The incidence of side effects at this dosage are similar to placebo.

Keywords colestipol hypercholesterolaemia dosage low density lipoprotein

Introduction

Bile acid sequestrants, including colestipol have suffered from a reputation of being awkward to take and frequently unpalatable particularly at the doses originally thought to be necessary to achieve significant LDL reduction, i.e. 20–30 g day⁻¹.

Studies using lower doses of colestipol (5–15 g day⁻¹), alone or in combination with probucol have demonstrated improved compliance with only a modest loss in efficacy [1, 2]. Nevertheless uncertainty still exists regarding

the optimal dosing regimen for these drugs. It has been reported that once a day administration of colestipol in the evening was comparable with two or more doses per day with meals and that each of these regimens were superior to once a day in the morning [3]. These results were further supported in a study examining once vs twice daily dosing with cholestyramine, where evening and twice daily dosing regimens were comparable but morning dosing was less effective [4]. This apparent

enhancement of efficacy with evening dosing may be explained by the circadian variation in cholesterol synthesis which is greatest around midnight [5].

This study was designed to test the effect, if any, of varying dosage regimens on the efficacy and tolerability of a total dose of 10 g colestipol daily in reducing LDL cholesterol levels in patients with moderate hypercholesterolaemia.

Methods

Patient selection

Patients were recruited from the combined hypertension/lipid clinic database on the basis of a known fasting total cholesterol level of ≥ 6.5 mmol l⁻¹. Moderate hypercholesterolaemia at entry was defined as a mean total cholesterol level of ≥ 6.5 mmol l⁻¹ taken at the first two visits of an initial 16 week dietary phase (1 month apart). Exclusion criteria included: familial hypercholesterolaemia, secondary hyperlipidaemia, hypertriglyceridaemia (≥ 2 mmol l⁻¹), diabetes mellitus, concurrent therapy with other lipid lowering agents, and the use of other medications that may have influenced lipid metabolism including steroids, oestrogens, fish oils and guar gum.

Study design

The design was that of a double-blind, placebo controlled, parallel group study. The study consisted of two parts, firstly a 16 week dietary phase followed by a 12 week active drug treatment phase. The drug or matched placebo (avicel), was administered as 5 g twice daily (COL am/pm) or 10 g once daily in the morning (COL am) or evening (COL pm) at fixed times (07.00–09.00 h and 17.00–19.00 h) with meals. Ninety-eight patients entered the initial 16 week dietary phase—American Heart Association Step 1 diet.

During both phases of the study patients attended the research clinic at 4 weekly intervals. Dietary advice was given by the same clinic dietician and reinforced at each visit throughout each phase. At the end of the dietary phase all 98 patients were eligible to enter the 12 week treatment phase (i.e. total cholesterol ≥ 6.0 mmol

l⁻¹ and ≤ 10.0 mmol l⁻¹, taken as the mean of two fasting measurements after 8 and 12 weeks of adherence to the AHA step 1 diet). Patients were then randomised to placebo or active treatment and to one of the three treatment schedules. Fasting lipid profiles were obtained following an overnight fast, every 4 weeks during both phases of the study. Compliance to the prescribed treatment regimen, was assessed by monitoring the number of packets of study medication dispensed and returned at each visit.

Statistics

The study had an 80% power to detect a 10% change in LDL with a two sided type 1 error probability of 0.05. Comparisons among treatment regimens with respect to percentage change from baseline values in the lipid variables were made using the one way ANOVA fixed effects model. In cases where the overall *F*-test indicated significant differences among the four treatment regimens (*P* < 0.05), pairwise comparisons were made using the least squares means approach.

Results

Patients who completed at least two of the three scheduled lipid profiles during the medication phase of the study, were considered evaluable for analyses of the response variables. Sixteen patients terminated early, 1 due to a protocol violation, 2 at their own request and 13 because of non-serious adverse effects (6: colestipol pm, 3: placebo).

There were no statistically significant differences among the treatment regimens with regard to age, sex, race and smoking status (Table 1). The treatment regimens also did not differ with regard to baseline LDL, total cholesterol, HDL and triglyceride levels. The baseline values and actual changes of total cholesterol, LDL, HDL and triglycerides are shown in Figure 1.

LDL cholesterol

All of the colestipol treatment regimens significantly reduced LDL compared with placebo (*P* = 0.0001)

Table 1 Age, sex, percentage compliance and mean incidence of reported adverse events in each treatment group (95% confidence intervals). Percentage compliance was assessed by the following formula: {(packets issued) – (packets returned)/(packets prescribed)} × 100.

	Colestipol am	Colestipol pm	Colestipol am/pm	Placebo
Age (range) (years)	53 (33–64)	56 (40–65)	53 (26–64)	56 (40–64)
Male	8	13	9	6
Female	16	12	15	19
% compliance	97.8	96.6	94.4	94.4
Mean incidence of adverse events per patient (95% CI)	1.2 (1.8–0.6)	2.0 (2.5–1.5)	2.3 (2.3–1.6)	2.4 (3.1–1.8)

Figure 1 Means (s.e. mean) of total cholesterol, LDL, HDL and triglyceride concentrations during the dietary (0–16 weeks) and drug treatment (16–24 weeks) phases. Colestipol am (Δ), colestipol pm (□), colestipol am/pm (○), placebo (▲).

(Figure 1). The percentage change from averaged base-line (weeks 8, 12 and 16 during the dietary phase) to averaged treatment value was also significant (COL am: 17%, COL pm: 18%, COL am/pm: 19% ($P = 0.0001$)). There were no statistically significant differences among the three colestipol treatment regimens (Figure 1).

Total cholesterol

All of the colestipol treatment regimens reduced total cholesterol compared with placebo ($P = 0.0001$) (Figure 1). The percentage changes from baseline were also significant (COL am: 10%, COL pm: 10%, COL am/pm: 12% ($P = 0.0001$)). With the exception of a marginally significant difference between the COL pm and the COL am/pm regimens ($P = 0.097$) at week 20, there were no significant differences between the three colestipol treatment regimens.

HDL cholesterol

HDL cholesterol rose significantly with COL am (5% ($P = 0.021$)) and COL am/pm (7% ($P = 0.002$)) when compared with placebo while a marginal increase was seen with COL pm (4% ($P = 0.063$)) (Figure 1). There were no significant differences between the three colestipol regimens.

Triglycerides

Overall the colestipol regimens caused an 8.9% increase in triglyceride levels when compared with placebo but the difference was not statistically significant. The actual changes are presented in Figure 1.

Dietary intervention

Total cholesterol fell by 5.6%, from 7.3 to 6.9 mmol l⁻¹ in the 98 patients who completed the dietary phase of the study ($P = 0.0001$). However the fall was not significant for the 82 patients in the same dietary phase who proceeded to the active treatment part of the study.

Compliance

The percentage compliance with each treatment regimen, is presented in Table 1.

Medical events

The average incidence of reported adverse events in each treatment group (95% confidence intervals) are listed in Table 1. The most frequently reported medical events were flatulence, constipation, nausea and abdominal discomfort. The COL am regimen had significantly fewer ($P = 0.02$) patients reporting medical events than other regimens.

Discussion

The bile acid sequestrants are drugs of first choice for initial therapy in familial hypercholesterolaemia and other forms of diet resistant hypercholesterolaemia [6]. The safety and efficacy of these drugs have been conclusively demonstrated but inconvenience and poor palatability have resulted in significant compliance problems, particularly at the doses initially prescribed.

Continued efficacy and better compliance have been achieved at lower doses but uncertainty about the optimal dosing regimen persists [2, 7].

We have shown that colestipol granules 10 g daily, taken either as a single dose (morning or evening) or as a divided dose, twice daily for 12 weeks with meals, reduces LDL cholesterol by approximately 17% from baseline, compared with placebo in patients on AHA step 1 diet. There were no clinically significant differences between the treatment regimens with regard to efficacy. These data support a recommendation of flexibility in dosage schedule with meals which may be of more convenience to the patient.

The expected increase in triglyceride levels with a bile acid sequestrant was seen and we would advise against its use in those with raised triglyceride concentrations [8].

Patient compliance in all groups exceeded 94%. Compliance measured in the context of a clinical study may not be predictive of what may happen in clinical practice but results suggest that the dosing regimens studied should be equally acceptable to patients.

The colestipol am group had significantly fewer

reported medical events than all other active treatment groups. The possible reasons for the apparent superiority of this regimen are unknown.

For all the patients entering the dietary phase, dietary intervention alone (AHA step 1) resulted in a significant reduction in total cholesterol of 5.6% which is superior to the results obtained with this diet in most other large studies [9]. These were a highly motivated group of patients and the level of dietary reinforcement at monthly intervals by the same dietician was greater than could realistically be achieved in a non-study setting.

In summary, low dose colestipol (10 g) taken either as a single or divided dose with meals according to the patients' preference is an effective and acceptable lipid lowering agent in patients already established on the AHA step 1 diet.

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References

- 1 Dujovne CA, Chernoff SP, Krehbiel P. Low dose colestipol plus probucol for hypercholesterolaemia. *Am J Cardiol* 1984; **52**: 514-518.
- 2 Superko HR, Greenland P, Manchester RA, *et al.* Effectiveness of low dose colestipol therapy in patients with moderate hypercholesterolaemia. *Am J Cardiol* 1992; **70**: 135-140.
- 3 Stein EA. Management of hypercholesterolaemia: Approach to diet and drug therapy. *Am J Med* 1989; **87** (4A): 20s-27s.
- 4 Hunninghake DB, *et al.* Efficacy of one versus twice-a-day dosage of cholestyramine in type IIa hyperlipoproteinemia. *Pharmacologist* 1979; **21**: 176.
- 5 Dempsey ME. Regulation of steroid biosynthesis. *Ann Rev Biochem* 1975; **44**: 967-972.
- 6 A policy statement of the European Atherosclerosis Society. The recognition and management of hyperlipidaemia in adults. *Eur Heart J* 1988; **9**: 571-600.
- 7 Witztum JL. Current approaches to drug therapy for the hypercholesterolemic patient. *Circulation* 1989; **80**: 1101-1114.
- 8 Lipid Research Clinics Programs. The Lipid Research Clinics Coronary Primary Prevention Trial Results I. Reduction in incidence of coronary heart disease. *J Am med Ass* 1984; **251**: 351-364.
- 9 Ramsay LE, Yeo WW, Jackson PR. Dietary reduction of serum cholesterol concentration: time to think again. *Br med J* 1991; **303**: 953-957.

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