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Original articles

Comparative efficacy and safety of ciprofibrate and sustained-release bezafibrate in patients with type II hyperlipidaemia

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Summary

The hypolipidaemic efficacy and safety of ciprofibrate were compared with a sustained-release formulation of bezafibrate (Bezalip Mono) in 174 patients with type II hyperlipidaemia. This multicentre, open, parallel-group study was conducted in general practice. A total of 83 patients received 100 mg ciprofibrate once daily and 91 received 400 mg bezafibrate once daily for eight weeks. Concentrations of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured at baseline (after stabilisation on a lipid-lowering diet) and after eight weeks. Safety was assessed from reports of adverse events and by measuring haematological and biochemical parameters. After eight weeks, ciprofibrate produced a significantly greater decrease in total cholesterol (−17.8% *vs* −12.5%), low-density lipoprotein cholesterol (−22.4% *vs* −17.2%), and triglycerides (−33.9% *vs* −26.1%). High-density lipoprotein cholesterol concentrations were increased significantly by both drugs (19.6% with ciprofibrate, 24.9% with bezafibrate) but the differences between drugs were non-significant. Both drugs were well tolerated, with headache the most widely reported adverse event.

Keywords: ciprofibrate, bezafibrate, hyperlipidaemia type II, hypolipidaemic agents

Increasing concentrations of serum cholesterol, and particularly low-density lipoprotein (LDL) cholesterol, are a major risk factor for coronary heart disease.[1–3] In the past the association between cholesterol and coronary heart disease has been underestimated because of regression dilution bias and surrogate dilution effect.[4] After correction for these factors it has been calculated from international studies that a difference in serum cholesterol concentrations of 0.6 mmol/l is associated with a reduction in the risk of coronary heart disease of 25–30%.[4] Most of the international variance in coronary heart disease can be explained by differences in serum cholesterol. Analysis of the observational cohort studies shows that a difference of 0.6 mmol/l in serum cholesterol is associated with a difference in mortality from coronary heart disease of 54% at age 40 years and 39% at age 50 years.[4] The controlled clinical trials of cholesterol lowering support the epidemiological data with a 25% reduction in coronary heart disease for a 0.6 mmol/l cholesterol reduction after five years.[5] Strong support for the benefits of reducing cholesterol concentrations has come from a recent secondary prevention trial using the hydroxy-methylglutaryl coenzyme A reductase inhibitor, simvastatin.[6] In this trial, the relative risk for death due to coronary heart disease in the treated group was 0.58 (95% CI 0.46–0.73).

Coronary heart disease risk prediction in the individual is improved with knowledge of the circulating concentrations of high-density lipoprotein (HDL) cholesterol, and triglycerides. Data from the PROCAM study[7] and the placebo group of the Helsinki Heart Study[8] point to the high risk of coronary heart disease in individuals with LDL/HDL ratios greater than five and with hypertriglyceridaemia. The major beneficial effect of the fibrate gemfibrozil in the Helsinki study was seen in this patient group.[8]

In previous studies both ciprofibrate[9–15] and bezafibrate[16–19] have effected reductions in triglyceride and LDL-cholesterol levels and increases in HDL-cholesterol levels; these studies give indirect evidence that ciprofibrate is a more potent lipid-lowering agent than bezafibrate. In the present study the efficacy and safety of ciprofibrate (100 mg) and a sustained-release formulation of bezafibrate (Bezalip Mono, 400 mg) were directly compared in patients with type IIa or IIb hyperlipidaemia in order to confirm this evidence.

Patients and methods

PATIENTS

The study was a randomised, open, parallel-group study performed in general practice.

Indications for treatment

- ciprofibrate: primary hyperlipidaemia resistant to appropriate dietary management, including hypercholesterolaemia, hypertriglyceridaemia and combined hyperlipidaemia (including types IIa, IIb, III and IV)
- bezafibrate: hyperlipidaemias of type IIa, IIb, III, IV and V

Box 1

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Patients were selected from those identified as being hyperlipidaemic during routine consultations at their general practice. A total of 346 patients were screened, of whom 190 were eligible for randomisation, with data from 174 patients (76 men and 98 women with an average age of 56 years) being statistically analysed. All patients had Fredrickson type II primary hyperlipidaemia (cholesterol $\geqslant$ 6.5 mmol/l) and were within 25% of their ideal weight according to Metropolitan Life standard insurance tables. One hundred and seventeen (58 on ciprofibrate, 59 on bezafibrate) of the patients in the study had type IIa hyperlipidaemia (cholesterol $\geqslant$ 6.5 mmol/l, triglycerides $<$ 2.3 mmol/l). The remaining 57 patients (25 ciprofibrate, 32 bezafibrate) had type IIb hyperlipidaemia (cholesterol $\geqslant$ 6.5 mmol/l, triglycerides between 2.3 and 4.5 mmol/l). The range of LDL-cholesterol values was 3.9–7.0 mmol/l for the ciprofibrate group and 4.3–8.0 mmol/l for the bezafibrate group. There were 11 patients randomised to ciprofibrate and 17 to bezafibrate who had an LDL-cholesterol level below 5.0 mmol/l at baseline. Only one patient (ciprofibrate group) had a level below 4.0 mmol/l. An expert report on the treatment of high blood cholesterol in adults[20] has stated that it is desirable for LDL-cholesterol levels to be below 3.4 mmol/l. Levels between 3.4 and 4.1 mmol/l are associated with a borderline high risk of coronary heart disease, depending upon the presence of other risk factors, and patients with LDL-cholesterol levels above 4.1 mmol/l are considered at high risk of coronary heart disease.

None of the patients had clinically significant hepatic, renal or endocrine disease. Patients who had suffered myocardial infarction or other acute vascular incident within three months prior to the baseline stabilisation period, who had overt cardiac failure or cardiac decompensation, or who required anticoagulant therapy were excluded from the trial. Women taking oral contraceptives, or who were lactating, pregnant or intending to conceive, were also excluded. Patients taking drugs that might influence lipid concentrations (eg, diuretics or beta-blockers) were allowed into the trial providing they had been on chronic stable dosage for the previous three months. No patients had taken any lipid-lowering drugs for six weeks (six months for probucol) before entry. After baseline stabilisation, 83 patients were randomised to ciprofibrate (100 mg once daily) and 91 patients to bezafibrate (400 mg once daily). All treatment was taken for eight weeks.

STUDY DESIGN

Patients underwent an initial six-week pre-study screen and were instructed by their general practitioners to adhere to the standard lipid-lowering diet recommended by the European Atherosclerosis Society[21] throughout the study. Compliance with diet was checked by questionnaire periodically during the study. This was followed by a four-week baseline stabilisation period during which dietary compliance was confirmed and eligibility for entry into the study was re-assessed. If during this period total cholesterol concentrations fluctuated by more than 15%, or triglyceride concentrations by more than 20%, patients underwent a further four weeks of baseline stabilisation and were then re-assessed for entry into the study. Patients were randomised according to a code generated by SAS® software (SAS Institute Inc, Cary, NC). A full clinical and cardiovascular examination was performed following the pre-study screen. Lipid concentrations, haematological and biological parameters were analysed after the pre-study screen, baseline stabilisation, and after four and eight weeks of treatment. Study treatment was given with the evening meal.

ETHICAL CONSIDERATIONS

Approval for the study was given by the Royal College of General Practitioners Ethics Committee. Each investigator obtained approval from their local ethics committee before commencing the study. The trial was monitored according to Good Clinical Practice. The study was conducted in accordance with the Declaration of Helsinki and each patient gave written informed consent prior to enrolment into the study.

LABORATORY METHODS

Blood samples were obtained after an overnight fast and analysed by a central laboratory. In-house testing by the central laboratory confirmed that the analytes measured were stable for up to three days at ambient temperature. Total serum cholesterol and triglycerides were measured using an ICSI Summit Analyser. HDL-Cholesterol was measured after precipitation of VLDL- and LDL-cholesterol with dextran sulphate–$MgCl_2$.[22] The coefficient of variation of the laboratory assays was less than 3% for total cholesterol and triglycerides, and less than 5% for HDL-cholesterol. LDL-Cholesterol was calculated from triglyceride, total and HDL-cholesterol values using the Friedewald formula.[23] Biochemical and haematological safety parameters were measured.

STATISTICAL ANALYSIS

Allowing for a drop-out rate of one in three, the number of patients required to show a difference of 8.3% or more between treatments in the percentage reduction in total cholesterol with 90% power, was calculated to be 200. Analysis of covariance on percentage change from baseline was performed for each group following eight weeks of treatment. Mean values are presented on raw data but p-values refer to the analysis of covariance, which takes into account variation in baseline values and between centres. Results were deemed significant if $p \leqslant 0.05$.

Results

One hundred and ninety patients fulfilled entry criteria and were randomised to treatment (90 ciprofibrate, 100 bezafibrate). Sixteen patients (seven ciprofibrate, nine bezafibrate) were

Table 1 Demographic data for each treatment group

		Ciprofibrate (n=83)	*Bezafibrate (n=91)*
Sex distribution (m/f)		34/49	42/49
Age (years)	mean (SD)	56.30 (9.27)	56.50 (8.40)
	range	25–69	35–70
Weight (kg)	mean (SD)	72.50 (13.14)	72.10 (11.40)
	range	50–111	42–96

excluded because no fasting lipid results at baseline or week eight were available or because of incorrect randomisation. Twenty-three patients in each group were receiving concomitant medications that may have influenced lipid concentrations. The demographic data at entry into the study are given in table 1.

No changes in mean body weight were observed throughout the study.

EFFICACY AFTER EIGHT WEEKS OF TREATMENT

Both treatment groups were well matched for lipid concentrations at baseline. Compliance with treatment as assessed by tablet count and overall mean compliance was 96.7% for ciprofibrate and 97.7% for bezafibrate. Changes in lipid parameters following eight weeks of treatment with ciprofibrate and bezafibrate are shown in table 2. Ciprofibrate 100 mg caused a significantly greater reduction in total cholesterol, LDL-cholesterol, and triglycerides than bezafibrate 400 mg. Both drugs caused a significant increase ($p=0.0001$) in HDL-cholesterol concentrations, but the difference between the drugs was not statistically significant.

Decreases in LDL-cholesterol with concomitant increases in HDL-cholesterol produced favourable changes in the LDL/HDL-cholesterol ratio for both treatments. Ciprofibrate gave a mean reduction in the LDL/HDL ratio of 1.74 compared with a reduction of 1.63 for bezafibrate, although the difference was not significant.

The percentage change in total cholesterol, LDL-cholesterol, HDL-cholesterol and serum triglycerides differed between the sexes, females having a larger response than males with both treatments. The differences were not statistically different as determined by a test of treatment-by-sex interaction. However, the study was not designed to determine such sex differences.

Comparisons of changes in lipid parameters between type IIa and IIb hyperlipidaemics are shown in table 3. In all cases differences between drugs and between type IIa and IIb patients were nonsignificant. For both treatments, a greater percentage reduction from baseline in total serum cholesterol and LDL-cholesterol was seen in type IIa patients compared with type IIb patients. Decreases in

Table 2 Mean (SD) lipid concentrations and percentage change from baseline after eight weeks treatment with ciprofibrate or bezafibrate

Lipid parameter (mmol/l)	*Ciprofibrate*			*Bezafibrate*			*Difference (% change) between treatments (p)*
	Baseline	*8 weeks*	*% change*	*Baseline*	*8 weeks*	*% change*	
Total cholesterol	7.78 (0.71	6.35 (0.89)	−17.8 (11.8)	7.70 (0.80)	6.71 (0.94)	−12.5 (11.7)	0.0008
n	83	81	81	91	91	91	
Triglycerides	2.01 (0.83)	1.27 (0.61)	−33.9 (22.2)	1.96 (0.79)	1.39 (0.58)	−26.1 (24.9)	0.027
n	82	82	81	91	91	91	
LDL-cholesterol	5.67 (0.69)	4.35 (0.89)	−22.4 (15.4)	5.62 (0.81)	4.59 (0.87)	−17.2 (16.6)	0.016
n	78	80	77	88	89	86	
HDL-cholesterol	1.19 (0.33)	1.42 (0.36)	19.6 (19.0)	1.21 (0.33)	1.48 (0.38)	24.9 (20.7)	0.058
n	79	81	78	88	89	86	

Table 3 Mean (SD) percentage change in lipid parameters from baseline following eight weeks of treatment with ciprofibrate or bezafibrate. Patients classified according to type IIa or IIb hyperlipidaemia

	Type IIa hyperlipidaemia		*Type IIb hyperlipidaemia*	
	Ciprofibrate	*Bezafibrate*	*Ciprofibrate*	*Bezafibrate*
Total serum cholesterol	−18.8 (12.4)	−13.7 (10.5)	−15.5 (10.3)	−10.2 (13.5)
n	56	58	25	32
Total serum triglycerides	−31.7 (23.9)	−24.3 (24.7)	−39.2 (16.9)	−29.5 (25.3)
n	57	58	25	32
LDL-cholesterol	−25.0 (15.3)	−20.2 (14.1)	−15.9 (13.9)	−11.7 (19.5)
n	56	59	24	31
HDL-cholesterol	18.8 (19.3)	23.1 (19.4)	21.9 (18.4)	28.3 (23.0)
n	57	59	24	31

total serum triglycerides, and increases in HDL-cholesterol, were greater for type IIb patients with both treatments.

The group randomised to ciprofibrate 100 mg/day were continued on treatment for an additional eight weeks at a higher dosage of 200 mg/day. The concentrations of total serum cholesterol, LDL-cholesterol and serum triglycerides were further reduced to 5.85 mmol/l, 3.88 mmol/l and 1.20 mmol/l, respectively. Changes in total serum cholesterol and LDL-cholesterol were significantly different ($p=0.0001$ in both cases) from week eight results. The mean concentration of HDL-cholesterol (1.41 mmol/l) was slightly, although not significantly, reduced from that observed at week eight.

TOLERABILITY

A total of 19 adverse events considered likely to be related to study drug were reported by 13 patients during the eight-week trial period. Six patients on ciprofibrate reported nine events and seven patients on bezafibrate reported 12 events, with headache the most common event. None of these events was severe. Four of these patients (two from each treatment group) withdrew from the study because of adverse events. Withdrawals were due to alopecia (ciprofibrate), somnolence combined with fever (ciprofibrate), headache (bezafibrate), and a combination of rash, nausea, vomiting and oedema (bezafibrate). Another two patients from each group withdrew for reasons not considered likely to be related to study drug.

There were no clinically significant changes (more than three times the upper limit of normal) in urea, creatinine, aspartate aminotransferase, or alanine aminotransferase, or in any haematological parameters during treatment with either drug.

A large decrease in alkaline phosphatase concentrations was observed with both treatments. The only major difference between treatments was a significant increase ($p=0.0001$) in creatine phosphokinase concentrations on ciprofibrate. The rise at week eight compared to baseline was 29.6%, compared with 5.3% for bezafibrate. The range of creatine phosphokinase concentrations after eight weeks was 25–283 IU/l for ciprofibrate and 24–212 IU/l for bezafibrate; none of the increases was reported as clinically significant (normal range 15–130 IU/l).

Dose and side-effects

Ciprofibrate:
- one 100 mg tablet per day
- nine side-effects reported by six patients (most common being headache)
- two side-effects led to withdrawal of patients (alopecia and somnolence combined with fever)
- no events were classed as severe

Bezafibrate:
- one 400 mg modified release tablet per day
- twelve side-effects reported by seven patients (most common being headache)
- two side-effects led to withdrawal of patients (headache and a combination of rash, nausea, vomiting and oedema)
- no events were classed as severe

Box 2

Learning/summary points

Comparison of ciprofibrate with sustained-release bezafibrate
- ciprofibrate gave significantly greater reductions in total- and LDL-cholesterol, and triglycerides
- HDL-cholesterol levels were increased with both drugs
- both drugs were well tolerated with similar side-effect profiles
- a substantial reduction in coronary heart disease risk would be expected from the observed changes in lipid profile

Box 3

Discussion

This study is the first direct comparison between ciprofibrate and Bezalip Mono. The major finding was that ciprofibrate treatment was associated with significantly greater reductions in total cholesterol, total triglycerides and LDL-cholesterol. HDL-Cholesterol increased with both drugs but there was no statistical difference between the two drugs. Differences in efficacy between the drugs could not be accounted for by differences in compliance or lifestyle changes during the trial. The magnitude of the lipid changes observed are similar to previous reports except for the increases in HDL-cholesterol, which were higher for both drugs in this study.[24–26] The explanation for these differences is not clear, although the preponderance of females may partly explain the higher increases in HDL-cholesterol observed in this study. Increasing the dose of ciprofibrate to 200 mg daily for a further eight weeks, led to further significant reductions in cholesterol, triglycerides and LDL-cholesterol but not HDL-cholesterol.

The modes of action of the fibrate class of drugs remain to be fully determined and there is likely to be considerable heterogeneity of effect with the different drugs. The best described effect of fibrates is the increase in activity of lipoprotein lipase, which is important in the hydrolysis of triglyceride-rich particles. During this process, surface components from the triglyceride-rich particles transfer to the HDL fraction. Other effects may include decreased hepatic lipoprotein production and increased clearance of LDL-cholesterol. In this study both drugs produced similar effects in patients with type IIa and type IIb hyperlipidaemia, although effects on triglycerides and HDL-cholesterol were slightly greater in the IIb patients and effects on total cholesterol and LDL-cholesterol slightly less.

The LDL/HDL-cholesterol ratio was significantly reduced by both drugs and the reduc-

tion observed with ciprofibrate (5.1 to 3.3) confirms the findings of an earlier study by Illingworth *et al*[9] who observed a change in the ratio from 5.1 to 3.5.

Both drugs were well tolerated. Only two patients from each treatment group withdrew from the study because of adverse events considered likely to be related to study drug. Increases in creatine phosphokinase concentrations have been observed previously in studies of fibrates and HMG-CoA reductase inhibitors.[27,28] In this study there was a significantly greater increase in creatine phosphokinase with ciprofibrate, but the changes were not associated with symptoms and no clinically significant elevations were observed. There were no cases of myositis. As expected, alkaline phosphatase concentrations were decreased.

Recent results from the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT) reported in *Scrip* show that progression of atheroma was significantly reduced by bezafibrate. It remains to be shown whether more potent fibrates, such as ciprofibrate, will have a greater effect in regressing atherosclerotic plaques, due to their more marked LDL-lowering ability compared with bezafibrate.

In summary, both drugs produced beneficial changes in the plasma lipid profile. Based on current available information it is believed that these changes would be associated with a substantial reduction of coronary heart disease risk. Ciprofibrate was significantly more effective in reducing cholesterol, triglycerides and LDL-cholesterol.

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