Efficacy of micronised fenofibrate in patients with primary hyperlipidaemia: a comparison with pravastatin

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Abstract

This randomised, double-blind, six-month trial assessed the efficacy and tolerability of micronised fenofibrate and pravastatin in 265 patients (18–75 years of age) with primary hyperlipidaemia (pure hypercholesterolaemia, type IIa; and mixed dyslipidaemia, type IIb) recruited from 28 European centres. After a first three-month phase in which patients received once daily either micronised fenofibrate 200 mg or pravastatin 20 mg, type IIa patients attaining low density lipoprotein cholesterol (LDL) < 4.14 mmol/L and type IIb patients attaining LDL < 4.14 mmol/L and triglycerides < 2.26 mmol/L continued with the same dose in a three-month extension phase. Patients not meeting these criteria received a double dose of drug in this extension phase.

Micronised fenofibrate and pravastatin were similarly effective in reducing levels of LDL and total cholesterol in patients with pure hypercholesterolaemia and mixed dyslipidaemia in the initial three-month phase, although high density lipoprotein cholesterol (HDL) levels were increased, and triglycerides were reduced, by a significantly greater degree by micronised fenofibrate (p=0.0001 and p=0.0011, respectively).

In the extension phase, in the constant-dosage groups, both treatments maintained their effect in reducing LDL, while micronised fenofibrate maintained the triglyceride reduction more effectively than pravastatin. In the increased dosage group, continued LDL reductions were attained with both treatments, while the patients receiving micronised fenofibrate showed a significantly greater triglyceride reduction than the pravastatin patients.

Treating patients with a new generation fibrate for primary hyperlipidaemia produces LDL and cholesterol-lowering benefits comparable to statin therapy, and has the added advantages of significant triglyceride reduction and a possibly more effective HDL-raising ability.

Key words: cholesterol, dyslipidaemia, fenofibrate therapy, hypercholesterolaemia, statin therapy.

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Introduction

The fibrates (fibric acid derivatives) and the statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) constitute the main pharmacological approaches to the management of dyslipidaemia. The effects of fibrates are mediated, at least in part, through the modified transcription of protein-encoding genes involved in lipoprotein metabolism.[1] The nuclear hormone receptor, peroxisome proliferator-activated receptor-alpha (PPARα), which is activated by fibrates, has a central role in this process. Statins inhibit cholesterol biosynthesis by competitively inhibiting HMG-CoA reductase (the enzyme that catalyses the conversion of HMG-CoA to mevalonate, a precursor of sterols, including cholesterol).[2] This suppression of cholesterol biosynthesis produces an up-regulation of low density lipoprotein cholesterol (LDL) receptors in the liver and an enhanced clearance of LDL from the plasma.

The increased bioavailability of the active compound in 'micronised' fenofibrate – an advanced formulation[3] – enables the drug to decrease LDL and total cholesterol, and to produce a marked reduction in elevated plasma triglyceride (TG) levels, and a substantial increase in high density lipoprotein cholesterol (HDL) levels.[4] Pravastatin consistently produces reductions in both LDL and total cholesterol levels that are dose-dependent, but its effects on other lipid levels, such as triglycerides and HDL, are generally less substantial and unrelated to dose.[5]

The results of previous trials with statins clearly show their benefit in preventing both fatal and non-fatal coronary events, mainly through this significant reduction in LDL.[6-10] For all patients with dyslipidaemia, therefore, statins have normally been regarded as the drugs of choice. A contrasting viewpoint, however, is that intervention to correct the effects of dyslipidaemia should not focus on LDL alone, and that the role of the other lipid fractions should be regarded also as potentially significant in risk manage-

ment. Support for this view comes from these same statin trials: while the expected level of reduction in major coronary events achieved may be approximately 30–35%, there still remains a high proportion (around two thirds) of at-risk patients who experience a cardiovascular event, despite the LDL reduction. The significance of the normalisation of other lipid fractions (HDL, triglycerides, apo B) and the correction of other non-lipid parameters may, therefore, have been previously undervalued. Results from recent trials provide compelling evidence that a low level of HDL is an independent risk factor for coronary heart disease (CHD),[11-13] and, therefore, that HDL normalisation should be a therapeutic target in the management of dyslipidaemia. Similarly, the possible importance of normalised triglyceride levels in conferring additional risk protection should not be underestimated.

Although the superior efficacy of fibrates in reducing triglycerides is well established and documented,[4] the comparative efficacy of fibrates and statins in increasing levels of HDL and lowering LDL has not been established.

The main overall objective of this study was to determine the efficacy and tolerability of micronised fenofibrate 200 mg and pravastatin 20 mg in patients with primary hyperlipidaemia. Its primary objective was to compare the efficacy of these agents in LDL reduction in patients with primary hyperlipidaemia – pure hypocholesterolaemia (type IIa) and mixed dyslipidaemia (type IIb) – and their relative efficacy in lowering triglycerides and raising HDL in patients with mixed dyslipidaemia after three months of treatment.

An extension to the study of an additional three months was made in order to assess whether the outcomes observed continued beyond the initial phase, and whether maintaining or increasing the drug dose affected the outcomes. The statin pravastatin was used in this investigation since it was one of the few appropriate comparators available at the time the study was initiated. The dose levels used in the trial reflect those considered appropriate at that time, prior to the introduction of other statin formulations and modified standard dosages. Similarly, doubling the statin and fenofibrate dose levels to 40 mg and 400 mg, respectively, in patients who had shown a weak response to treatment over the first three-month phase of the study was considered appropriate in the context of this study design.

Methods

Study design and patients

A total of 265 male and female patients (18-75 years of age) from 28 European centres were recruited into this prospective, parallel group, double-blind study. All had primary hyperlipidaemia, classified as pure hypercholesterolaemia (total cholesterol $\geq$ 6.48 mmol/L, total triglyceride < 2.26 mmol/L) or mixed dyslipidaemia (total cholesterol $\geq$ 6.48 mmol/L, 2.26 mmol/L $\leq$ total triglyceride < 4.52 mmol/L). The study comprised a three-month run-in period on a fat-modified American Heart Association (AHA) step 1 diet, followed by two successive three-month treatment phases.

Patients with a history of pancreatitis, cholestasis or hepatic malfunction, those with active gastroduodenal ulcers during the last three months, diabetes mellitus, untreated or unstable hypothyroidism, obesity, recent angina, myocardial infarction, cardiac surgery or cerebrovascular accident, obvious abnormalities of cardiovascular function or impaired renal function were excluded. After the dietary run-in period, patients whose lipid levels no longer met the inclusion criteria were excluded, as were those who had taken oral anticoagulants, cyclosporin, fluoxetine, probucol and any medication that could influence lipid metabolism (including standard oral contraceptives and omega-3 polyunsaturated fatty acids).

Table 1. Demographic data at baseline (mean±SD or n [%])

	Fenofibrate (n=75)	Pravastatin (n=76)	Total (n=151)
Female	27 (36.0%)	31 (40.8%)	58 (38.4%)
Male	48 (64.0%)	45 (59.2%)	93 (61.6%)
Weight (kg)	73.3±13.2	75.0±11.1	74.1±12.2
Height (cm)	169.8±9.1	169.4±9.4	169.6±9.2
Age (years)	54.0±12.2	53.6±13.2	53.8±12.7
BMI (kg/m^2)	25.3±3.2	26.1±2.8	25.7±3.1
Types of dyslipidaemia			
● IIa	45 (60.0%)	43 (56.6%)	88 (58.3%)
● IIb	27 (36.0%)	33 (43.4%)	60 (39.7%)
● Other	3 (4.0%)	0	3 (2.0%)

At entry to phase I, patients were randomised to treatment with either micronised fenofibrate (200 mg once daily) or pravastatin (20 mg once daily). At the end of phase I, patients with pure hypercholesterolaemia whose LDL had fallen below 4.14 mmol/L entered an extension phase (phase II) without any change in treatment. The criteria for entry into phase II for patients with mixed dyslipidaemia were: LDL < 4.14 mmol/L and triglycerides < 2.26 mmol/L. Patients who did not meet these criteria received a double dose of the drug (micronised fenofibrate 400 mg daily or pravastatin 40 mg daily) on entry to phase II and during the following three months.

Laboratory measurements

Standard biochemical and haematological variables were determined at the participating centres. Haemostatic factors were determined at CHUV Laboratoire d'Hématologie de Lausanne. All lipid assays were carried out at a centralised laboratory (Hospital AZ St Jan, Brugge). Lipid assays and biochemical and haematological measurements were made at entry to the treatment phase, at three months and at six months.

Statistical methods

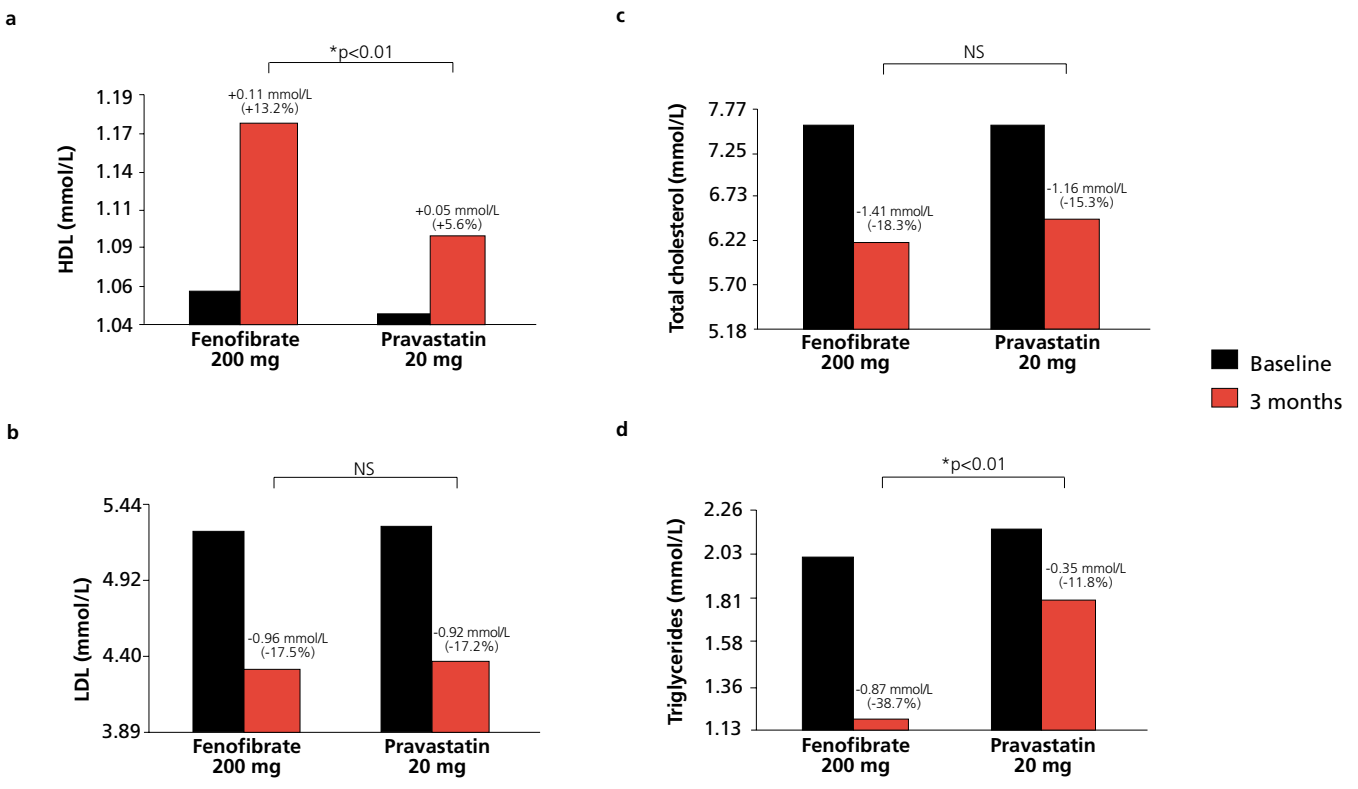
The main efficacy criterion for the type IIa dyslipidaemic patients was the difference in LDL value after three months, expressed as

Table 2. Lipid changes from baseline at three months (mean±SD)

	Fenofibrate (n=75)			Pravastatin (n=76)			
	Baseline (mmol/L)	3 months (mmol/L)	% change	Baseline (mmol/L)	3 months (mmol/L)	% change	p value**
HDL	1.06±0.32	1.17±0.31	13.2±21.7	1.04±0.29	1.10±0.31	5.6±17.6	p=0.0084
LDL calculated*	5.61±1.21	4.49±1.20	–19.2±18.2	5.62±1.20	4.53±1.17	–18.9±11.2	p=0.8939
LDL measured	5.26±1.09	4.30±1.14	–17.5±18.1	5.27±1.12	4.35±1.09	–17.2±11.7	p=0.9231
Total cholesterol	7.61±1.23	6.20±1.30	–18.3±12.7	7.62±1.12	6.50±1.23	–15.3±9.3	p=0.1046
Triglycerides	2.04±0.92	1.18±0.66	–38.7±23.1	2.17±1.09	1.82±1.00	–11.8±32.4	p=0.0001
Apo B	1.41±0.25†	1.12±0.29†	–19.9±16.4	1.43±0.30†	1.26±0.29†	–11.2±16.1	p=0.0005

Key: *n=73 in the pravastatin group; **comparisons between the two groups (% change, fenofibrate *vs.* pravastatin) were performed using a parametric test (ANOVA) in the case of normality and a non-parametric test (Wilcoxon rank-sum test) in the case of non-normality; †=ApoB units in g/L

Figure 1. Primary end point comparisons of lipid-modifying effects of micronised fenofibrate (200 mg) or pravastatin (20 mg) after three months of treatment on a) HDL; b) LDL measured; c) total cholesterol; d) triglycerides



Key: *p<0.01 *vs.* pravastatin (ANOVA or Wilcoxon rank-sum test)

the percentage change from baseline. For type IIb patients, two main efficacy criteria were defined: the difference in levels of LDL and triglycerides after three months, both expressed as the percentage change from baseline.

The study was designed to detect a difference between the fenofibrate group and the pravastatin group of at least 10% in LDL for type IIa dyslipidaemia and to detect either a difference of at least 10% in LDL or at least 15% in triglycerides, or both, for type IIb dyslipidaemia.

It was calculated that a minimum number of 192 compliant

Table 3a. Lipid changes in patients with pure hypercholesterolaemia (type IIa) from baseline after three months (mean±SD)

	Fenofibrate 200 mg (n=45)			Pravastatin 20 mg (n=43)			
	Baseline (mmol/L)	3 months (mmol/L)	% change	Baseline (mmol/L)	3 months (mmol/L)	% change	p value*
HDL	1.16±0.35	1.23±0.34	8.6±18.1	1.15±0.31	1.22±0.32	8.0±18.9	p=0.4205
LDL calculated	5.67±1.16	4.28±1.04	–24.1±12.7	5.83±1.23	4.70±1.29	–19.8±10.8	p=0.0922
LDL measured	5.38±1.01	4.13±1.02	–23.1±12.7	5.58±1.11	4.53±1.21	–19.3±11.4	p=0.1415
Total cholesterol	7.50±1.11	5.93±0.98	–20.5±10.0	7.60±1.15	6.47±1.32	–15.2±8.7	p=0.0096
Triglycerides	1.46±0.39	0.92±0.28	–34.3±21.1	1.36±0.44	1.21±0.45	–7.2±37.0	p=0.0001

Key: *comparisons between the two groups (% change, fenofibrate *vs.* pravastatin) were performed using a parametric test (ANOVA) in the case of normality and a non-parametric test (Wilcoxon rank-sum test) in the case of non-normality

Table 3b. Lipid changes in patients with mixed dyslipidaemia (type IIb) from baseline after three months (mean±SD)

	Fenofibrate 200 mg (n=27)			Pravastatin 20 mg (n=33)			
	Baseline (mmol/L)	3 months (mmol/L)	% change	Baseline (mmol/L)	3 months (mmol/L)	% change	p value**
HDL	0.91±0.17	1.10±0.25	22.0±25.7	0.91±0.18	0.94±0.23	2.6±15.6	p=0.0011
LDL calculated*	5.55±1.34	4.82±1.35	–11.5±23.1	5.31±1.12	4.34±0.96	–17.6±11.7	p=0.2213
LDL measured	5.04±1.23	4.57±1.24	–7.9±22.1	4.87±1.01	4.13±0.87	–14.6±11.6	p=0.1649
Total cholesterol	7.86±1.38	6.66±1.58	–15.0±15.8	7.65±1.10	6.45±1.11	–15.5±10.3	p=0.8886
Triglycerides	3.07±0.63	1.62±0.85	–46.7±25.5	3.22±0.69	2.61±0.95	–17.9±24.5	p=0.0001

Key: *n=30 in the pravastatin group; **comparisons between the two groups (% change, fenofibrate *vs.* pravastatin) were performed using a parametric test (ANOVA) in the case of normality and a non-parametric test (Wilcoxon rank-sum test) in the case of non-normality

patients (94 type IIa and 98 type IIb), having followed three months of treatment, would be required in order to test the null hypothesis of no difference between groups with a power greater than 90%.

Treatment groups were compared using, as appropriate, parametric or non-parametric methods (χ^2 test, Fisher's exact test, one-way analysis of variance, and Wilcoxon rank-sum test). The significance level was set at 5% (two-tailed).

All analyses were performed on the Full Analysis Set population using Last Observation Carried Forward (LOCF) lipid values. LOCF at three months corresponds to the last value registered during visits at one, two and three months.

Results

Following the run-in period, a total of 152 patients were randomised to treatment and included in phase I. One patient from the fenofibrate group was withdrawn after three days of treatment, having been mistakenly included in the group because of a laboratory error; consequently 151 patients (75 in the fenofibrate group, 76 in the pravastatin group) were included for analysis. The treatment groups did not differ significantly with respect to age, sex, height, weight or body mass index. Table 1 shows baseline demographics.

Efficacy

The overall results for the 151 patients after the first three months of treatment with micronised fenofibrate 200 mg or pravastatin 20 mg once daily are summarised in table 2. Absolute changes in HDL, LDL, total cholesterol and triglycerides are shown in figure 1.

Mean levels of LDL measured were reduced similarly by micronised fenofibrate 200 mg (-17.5%±18.1) and by pravastatin 20 mg (-17.2%±11.7). Both treatments were also equally effective at reducing total cholesterol (-18.3%±12.7 *vs.* -15.3%±9.3, respectively).

Mean levels of HDL were increased more effectively by micronised fenofibrate than by pravastatin (13.2% *vs.* 5.6%, p=0.0084). Similarly, micronised fenofibrate produced significantly greater reductions in triglycerides (-38.7% *vs.* -11.8%, p=0.0001) and apo B (-19.9% *vs.* -11.2%, p=0.0005) than did pravastatin. The decrease of triglycerides was three times greater with micronised fenofibrate than with pravastatin.

Table 4. Mean (±SD) lipid changes from baseline after three and six months (constant doses)

Fenofibrate 200 mg (n=33)					
	Baseline (mmol/L)	**3 months (mmol/L)**	**% change**	**6 months (mmol/L)**	**% change**
LDL measured	4.77±0.57	3.49±0.61	–26.5±13.4	3.36±0.52	–29.1±11.6
LDL calculated	5.12±0.54	3.65±0.65	–28.4±12.1	3.59±0.59	–29.5±11.8
Triglycerides	1.79±0.62	1.03±0.43	–39.1±25.4	0.96±0.36	–44.5±19.4
Pravastatin 20 mg (n=25)					
	Baseline (mmol/L)	**3 months (mmol/L)**	**% change**	**6 months (mmol/L)**	**% change**
LDL measured	4.79±0.53	3.56±0.34	–25.0±8.9	3.65±0.67	–23.8±11.4
LDL calculated*	5.05±0.56	3.70±0.38	–26.0±9.3	3.82±0.88	–24.3±15.3
Triglycerides	2.06±1.09	1.41±0.56	–26.3±18.4	1.75±0.89	–11.2±24.6

Key: *n=24
Comparisons: Fenofibrate 200 mg *vs.* pravastatin 20 mg on % change at six months (constant doses): LDL measured: p=0.0890; LDL calculated: p=0.1551; triglycerides: p=0.0001

Table 5. Mean (±SD) lipid changes from baseline after three and six months (increased doses)

Fenofibrate 400 mg (n=35)					
	Baseline (mmol/L)	**3 months (mmol/L)**	**% change**	**6 months (mmol/L)**	**% change**
LDL measured	5.51±1.20	4.93±0.90	-8.2±18.2	4.33±1.03	-19.2±21.5
LDL calculated	5.92±1.44	5.14±1.04	-10.4±19.7	4.58±1.19	-19.7±24.3
Triglycerides	2.37±1.12	1.37±0.84	-38.6±22.4	1.38±0.87	-37.0±29.2
Pravastatin 40 mg (n=43)					
	Baseline (mmol/L)	**3 months (mmol/L)**	**% change**	**6 months (mmol/L)**	**% change**
LDL measured	5.50±1.19	4.71±1.05	-13.8±11.0	4.16±1.10	-23.9±14.1
LDL calculated*	5.83±1.19	4.88±1.05	-15.8±11.2	4.44±1.12	-23.5±13.6
Triglycerides	2.23±1.08	2.02±1.07	-4.4±37.8	1.88±0.94	-9.7±41.6

Key: *n=41
Comparisons: Fenofibrate 400 mg *vs.* pravastatin 40 mg on % change at six months (constant doses): LDL measured: p=0.5073; LDL calculated: p=0.9253; triglycerides: p=0.0003

At the end of phase I, in the group of patients with pure hypercholesterolaemia (58.3%), measured LDL was reduced by 23% with micronised fenofibrate 200 mg, compared with a 19% reduction with pravastatin 20 mg (table 3a, p=0.1415, NS). In the mixed dyslipidaemia patients (39.7%) both treatments were equally effective in reducing measured and calculated LDL while micronised fenofibrate was markedly more effective than pravastatin in reducing triglycerides (p=0.0001) and elevating HDL (p=0.0011, table 3b).

At the end of phase I, the proportion of patients in the micronised fenofibrate group attaining the predetermined efficacy criteria (LDL measured < 4.14 mmol/L and triglycerides < 2.26 mmol/L for patients with mixed dyslipidaemia) was higher than in the group receiving pravastatin (45.6% *vs.* 37.5% respectively, p=0.332).

During the second three-month treatment phase, 136 patients were analysed after allocating treatment based on their LDL or triglyceride response at the end of phase I. The results for both the constant dose and increased dose groups for LDL and triglycerides are shown in tables 4 and 5.

In the constant dose groups, both micronised fenofibrate 200 mg and pravastatin 20 mg achieved their maximal effect on

Table 6. Mean (±SD) change from baseline at six months for total population (n=136)

	Total fenofibrate (n=68)			Total pravastatin (n=68)			
	Baseline (mmol/L)	6 months (mmol/L)	% change	Baseline (mmol/L)	6 months (mmol/L)	% change	p value**
LDL measured	5.15±1.01	3.86±0.95	–24.0±18.0	5.24±1.05	3.97±0.99	–23.9±13.1	p=0.3619
LDL calculated*	5.53±1.16	4.10±1.06	–24.4±19.8	5.54±1.07	4.21±1.08	–23.8±14.1	p=0.2576
Triglycerides	2.09±0.95	1.17±0.70	–40.6±25.0	2.17±1.08	1.83±0.92	–10.3±36.1	p=0.0001

Key: *n=65 in pravastatin group; ** comparisons (% change, fenofibrate *vs.* pravastatin)

Table 7. Adverse events: number of patients, n (%), with adverse events 'probably' or 'possibly' related to the study treatment

	Fenofibrate 200 & 400 mg (n=75)	Pravastatin 20 & 40 mg (n=76)
Patients reporting adverse events *	15 (20%)	10 (13.2%)
Digestive system	7 (9.3%)	3 (3.9%)
Body as a whole	3 (4%)	0
Metabolic and nutritional disorders	3 (4%)	3 (3.9%)
Nervous system	3 (4%)	2 (2.6%)
Musculoskeletal system	2 (2.7%)	1 (1.3%)
Skin and appendages	2 (2.7%)	1 (1.3%)
Cardiovascular system	0	1 (1.3%)

Key: *one patient could have reported more than one adverse event

LDL and triglycerides during the first three-month treatment phase. After the second three-month treatment phase, both agents remained equally effective in reducing mean LDL measured (-29.1% *vs.* -23.8%, p=0.0890). The marked reduction in triglyceride was maintained with micronised fenofibrate (-44.5%), while the effect of pravastatin was significantly smaller (-11.2%) (p=0.0001).

In the increased dosage groups, micronised fenofibrate 400 mg and pravastatin 40 mg were equally effective in reducing mean LDL. Both provided greater LDL reductions compared with phase I (measured LDL at six months -19.2% with fenofibrate *vs.* -23.9% with pravastatin, p=0.5073). Micronised fenofibrate 400 mg maintained the triglyceride reduction achieved after phase I more effectively than pravastatin 40 mg (-37.0% *vs.* -9.7%, p=0.0003).

Table 6 shows changes in LDL and triglycerides for the whole population after six months. Both micronised fenofibrate and pravastatin markedly reduced mean LDL by 24% (p=0.3619 for measured LDL, and p=0.2576 for calculated LDL), while the micronised fenofibrate group exhibited a significantly greater triglyceride reduction than the pravastatin group (-41% *vs.* -10%, p=0.0001). The majority of patients in each treatment group reached the pre-established criteria for LDL and triglycerides. Indeed, 71% of patients in the micronised fenofibrate group achieved the target level, compared with 50% of patients in the pravastatin-treated group (p=0.016).

Tolerability

Both drugs were generally well tolerated. One or more adverse events, probably or possibly related to treatment, were experienced by 25 of the 151 patients (table 7). The most frequently reported treatment-related adverse events were in the digestive system (seven for fenofibrate and three for pravastatin).

Three patients in the fenofibrate 200 mg group were withdrawn from the study because of probable or possible treatment-related events: two because of increased liver enzymes and one because of abdominal pain. One patient in the fenofibrate 400 mg group was withdrawn because of severe constipation.

Three patients were withdrawn from the pravastatin 20 mg group because of headache, muscle cramps with elevated CPK levels and insomnia, and one patient was withdrawn from the pravastatin 40 mg group because of abnormal weight gain.

The percentage of adverse events probably or possibly related to the study medication was slightly greater in the higher dose groups with both drugs.

CPK levels exceeded the normal limit three-fold in six patients in the fenofibrate group (three in the single-dose and three in the double-dose group) and two patients in the pravastatin group (one in the single-dose and one in the double-dose group). Results for one patient in the 200 mg fenofibrate group were invalidated because he had taken vigorous exercise (played squash) the previous day; in the 400 mg dose group, the results in two cases were considered anomalous because one patient was suffering trauma from a recent head injury and the other had recently undergone a surgical operation. Creatinine levels increased over 133 µmol/L but did not exceed 177 µmol/L in two patients receiving fenofibrate 200 mg and in three patients receiving fenofibrate 400 mg. Uric acid levels decreased only in fenofibrate-treated patients. Haemoglobin levels decreased moderately in 15 patients receiving fenofibrate and in five receiving pravastatin.

Key messages

- After three months treatment, micronised fenofibrate 200 mg and pravastatin 20 mg were equally effective at reducing LDL and total cholesterol
- After three months treatment, micronised fenofibrate 200 mg produced significantly greater reductions, compared with pravastatin, in triglycerides and apo B, and significantly greater increases in HDL
- After six months treatment, the reduction in LDL was maintained by continued treatment with micronised fenofibrate 200 mg or pravastatin 20 mg
- After six months treatment, the marked reduction in triglycerides was maintained with fenofibrate 200 mg, in contrast to pravastatin 20 mg, which had a significantly weaker effect
- Following treatment with increased dosages in the extension phase, significantly greater reductions in LDL-C were attained with both treatments. Micronised fenofibrate 400 mg was significantly more effective than pravastatin 40 mg in maintaining the triglyceride reduction achieved in the first phase
- After the six-month treatment period, 71% of patients in the micronised fenofibrate treatment group achieved the pre-established target levels for LDL and triglycerides, compared with 50% of patients in the pravastatin-treated group
- Treatment with a new generation fibrate reduces LDL and total cholesterol to a comparable degree to that attained with statin therapy, but with the further advantage of significantly reducing triglycerides, and the possible further benefit of a more effective HDL-raising effect

Discussion

The favoured drugs for lowering plasma cholesterol levels are generally considered to be the HMG-CoA reductase inhibitors, such as pravastatin. The risk of cardiovascular events is significantly lowered by a reduction in LDL level.[6-10] In a primary prevention population, treatment with pravastatin at a maximum dose of 40 mg/day resulted in a 26% decrease in LDL and a significant reduction in the incidence of myocardial infarction and cardiovascular disease-related mortality (West of Scotland Coronary Prevention Study).[7]

The present study, a prospectively designed, randomised, double-blind trial, has shown that for patients with pure hypercholesterolaemia and mixed dyslipidaemia, micronised fenofibrate is as effective as pravastatin in reducing levels of LDL and total cholesterol. After six months of treatment, both micronised fenofibrate and pravastatin reduced measured and calculated LDL in patients with primary hyperlipidaemia by 24%.

As anticipated, the reduction of triglycerides with micronised fenofibrate was marked and was significantly greater than with pravastatin. Similarly, micronised fenofibrate 200 mg had a substantially greater effect than pravastatin 20 mg in raising HDL (22.0% *vs.* 2.6% at 3 months, p=0.0011) in the patients with mixed dyslipidaemia, where baseline HDL levels were considerably lower.

The results of the second phase of treatment clearly highlight the most appropriate starting dosages, which are micronised fenofibrate 200 mg and pravastatin 20 mg. For patients who do not respond sufficiently, or who may require further LDL and total cholesterol reduction, doubling the dosage of both micronised fenofibrate and pravastatin, where dose licensing permits, appears to be effective and generally well tolerated. At the time of writing, the maximum dosages of the study drugs licensed in the UK are fenofibrate 267 mg (Lipantil®) and pravastatin 40 mg (Lipostat®). Fenofibrate is also available in modified-release form as Supralip® 160 mg, a directly equivalent dosage to Lipantil® 200 mg.

The results of this trial demonstrate that treating patients with primary hyperlipidaemia with a new generation fibrate produces the benefits of lowering LDL and total cholesterol to a degree equivalent to that effected by statin therapy. Moreover, fibrate has the further benefit of reducing triglyceride levels significantly. An additional clinical benefit with fibrate treatment is also possible, as a consequence of its greater effectiveness in raising HDL levels, compared with a statin. Micronised fenofibrate may, therefore, be considered as a first-line therapy in such patients, and especially for those patients with low levels of HDL and moderately elevated LDL. The appropriate starting dosage of micronised fenofibrate should be 200 mg, but for patients who do not respond, or for whom additional LDL lowering is required, an increased dosage appears to be an efficient – and generally well tolerated - option.

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