Micronized fenofibrate: a new fibric acid hypolipidemic agent

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Authors' objectives
To assess the efficacy and safety of fenofibrate in the management of hyperlipidaemias.

Searching
MEDLINE (from 1974 to October 1998) and Currents Contents were searched, and the bibliographies from identified studies were examined. In addition, the package inserts from the manufacturers were used to identify data.

Study selection
Study designs of evaluations included in the review
The inclusion criteria were not defined in terms of study design. The studies included were randomised controlled trials (RCTs) of parallel or crossover design, including double-blinded RCTs, and observational studies. The duration of the comparative studies ranged from 4 weeks to 1 year.

Specific interventions included in the review
Studies evaluating fenofibrate were eligible. Fenofibrate (regular or micronised formulation) was administered either alone in doses ranging from 100 to 400 mg/day, or in combination with colestipol. The controls used in the comparative studies were placebo, simvastatin, colestipol, atorvastatin, probucol, gemfibrozil, and pravastatin.

Participants included in the review
The inclusion criteria were not defined in terms of the participants. Patients with type IIa, IIb, III, and IV hyperlipidaemia were included. The participants included those with type II diabetes, primary hypercholesterolaemia, familiar combined hyperlipidaemia, familial dysbetapolipoproteinemia, familial hypercholesterolaemia, familiar heterozygous hypercholesterolaemia, and familial hypertriglyceridaemia.

Outcomes assessed in the review
Safety and efficacy were assessed. Efficacy was assessed using changes in the following lipid parameters: total cholesterol; triglyceride; high-density lipoprotein cholesterol; low-density lipoprotein cholesterol; very low-density lipoprotein cholesterol; and very low-density lipoprotein triglycerides.

How were decisions on the relevance of primary studies made?
The author does not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
No formal assessment of validity was undertaken.

Data extraction
The author does not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The following information was tabulated: author and year of study; sample size; regimen; study design; results; and adverse effects.

Methods of synthesis
How were the studies combined?
The studies were grouped according to the type of hyperlipidaemia examined and the type of study (comparative and non-comparative). The mean percentage changes in lipid parameters were calculated using the mean significant change from baseline for all included individual studies.

How were differences between studies investigated?
The author does not state how the differences between the studies were investigated.

**Results of the review**

Twenty-five RCTs (2,220 patients) and 51 non-comparative studies (3,218 patients) were included.

The results from the fenofibrate arms of the comparative trials were reported as mean percentage alterations from baseline.

**Total cholesterol.**

Fenofibrate decreased total cholesterol levels by 20% (range: 17 to 28) in type IIa hyperlipidaemias, by 20% (range: 14 to 25) in type IIb, by 24% in type III, and by 14% in type IV.

**Triglyceride.**

Fenofibrate decreased triglyceride concentrations by 33% (range: 24 to 38) in type IIa hyperlipidaemias, by 46% (range: 41 to 53) in type IIb, by 51% in type III, and by 53% in type IV.

**High-density lipoprotein cholesterol.**

Fenofibrate increased high-density lipoprotein concentrations by 12% (range: 10 to 15) in type IIa hyperlipidaemias, by 20% (range: 8 to 34) in type IIb, by 21% in type III, and by 15% (range: 14 to 15) in type IV.

**Low-density lipoprotein cholesterol**

Fenofibrate decreased low-density lipoprotein concentrations by 26% (range: 20 to 24) in type IIa hyperlipidaemias and by 23% (range: 6 to 35) in type IIb. The concentrations were increased by 6% (range: -9 to +20) in type IV hyperlipidaemias.

**Very low-density lipoprotein cholesterol.**

Fenofibrate decreased very low-density lipoprotein concentrations by 44% (range: 38 to 61) in type IIa hyperlipidaemias, by 51% (range: 48 to 53) in type IIb, by 63% in type III, and by 60% (range: 56 to 63) in type IV.

**Very low-density lipoprotein triglycerides.**

Fenofibrate decreased very low-density lipoprotein triglyceride levels by 34% in type IIa hyperlipidaemias, by 52% in type IIb, by 58% in type III, and by 61% (range: 59 to 63) in type IV.

The comparative trials did not present data for low-density lipoprotein triglycerides.

**Adverse events.**

Twelve of the 25 comparative RCTs included did not present data on adverse effects.

The authors reported that from the included studies and the manufacturer's data on file, 'a constellation of events probably causally related can be constructed including: hepatitis; cholelithiasis; cholecystitis; hepatomegaly; myalgia; myasthenia; rhabdomyolysis; photosensitivity; eczema; and allergic pulmonary alveolitis. The overall frequency of these events with long-term therapy are not well established but appear to be no more than 10% per event'.

The findings of 4 studies on cholesterol gallstone formation indicated that fenofibrate may predispose to cholesterol
cholelithiasis.

Drug interactions.

Four clinical trials and 1 case report revealed that fenofibrate can enhance the effect of oral anticoagulants.

One study indicated that myopathy was associated with combination statin-fenofibrate therapy.

Higher statin doses (pravastatin 40 mg/day, simvastatin 60 mg/day) may cause myotoxicity with symptoms.

Pregnancy and lactation.

The safety of fenofibrate in pregnant and lactating women has not been established, and few data are available on fenofibrate in paediatric populations.

Cost information

Results from two studies on cost-effectiveness were reported (see Other Publications of Related Interest nos.1-2). One study (based on 2 RCTs), reported that micronised fenofibrate was superior to simvastatin in terms of the short-term cost-effectiveness. The costs per patient, treated successfully over 12 weeks, were $316 for fenofibrate and $476 for simvastatin.

One study estimated that the cost per life-year saved ranged from $19,888 to $73,632 for 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, and from $16,955 to $59,488 for fibrates. The lifetime costs varied according to the patient population, the efficacy of each drug in modifying lipid concentrations, and the drug prices.

Authors’ conclusions

Fenofibrate reduced total serum triglycerides, total cholesterol and low-density lipoprotein cholesterol, and raised high-density lipoprotein cholesterol to clinically relevant degrees. The adverse effects of fenofibrate appeared to be similar to those of other fibrates and require routine monitoring (clinical, liver function). Long-term safety data are readily available from drug registries. Cost-effectiveness studies, which compared fenofibrate with other hypolipidaemics, demonstrated the benefits of using fenofibrate over simvastatin in types IIa and III hyperlipidaemia.

The need for dosage titration of the micronised preparation from 67 mg/day to a final dose of 200 mg/day is not supported by peer-reviewed literature, except in cases of renal impairment. Although the preliminary data on plaque regression are encouraging, published clinical studies evaluating the impact of fenofibrate on cardiovascular morbidity and mortality are awaited. Micronised fenofibrate is worthy of formulary inclusion.

CRD commentary

The aims were stated and the inclusion criteria were defined in terms of the interventions and outcomes. The inclusion criteria were not defined for participants or study design. Two relevant databases were searched, but the search strategy was not described and it was not reported whether any language restrictions were applied. In addition, the details were provided of the methods used to select the studies. Validity was neither formally assessed nor discussed.

Some relevant information on the primary studies was presented in tabular format, but no details were given of the methods used to extract the data. Data were pooled from the fenofibrate treatment arms of all studies, without weighting for sample size. Statistical heterogeneity was not assessed. The results were based on short-term follow-up, with all but one of the 25 RCTs having a follow-up period of less than 6 months. The evidence would have been of a higher quality had the author weighted the pooled data using sample size, and demonstrated the absence of heterogeneity between studies. As the author states, clinical studies evaluating the impact of fenofibrate on cardiovascular morbidity and mortality are required. The efficacy of fenofibrate compared with other therapies was not assessed. Hence, the comments on comparisons of fenofibrate with other therapies were not supported by the evidence presented in this review.
Implications of the review for practice and research

Practice: The authors state that fenofibrate reduces serum triglycerides, total cholesterol and low-density lipoprotein cholesterol, and raises high-density lipoprotein cholesterol to clinically relevant degrees. In addition, the adverse effects appear similar to other fibrates and require routine monitoring. The authors went on to state that treatment goals should be communicated to patients, and that micronised fenofibrate is worthy of consideration for formulary inclusion, as a substitute for clofibrate and, perhaps, for gemfibrozil.

Research: The authors state that clinical studies evaluating the impact of fenofibrate on cardiovascular morbidity and mortality are awaited.

Bibliographic details

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10534222

Other publications of related interest

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Subject indexing assigned by NLM

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.