Systematic review of the efficacy and safety of perhexiline in the treatment of ischemic heart disease

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Authors' objectives
To examine evidence on the effects and tolerability of perhexiline used in the treatment of ischaemic heart disease.

Searching
MEDLINE and Biological Abstracts were searched using the terms 'perhexiline' and 'Pexid'. The bibliographies of relevant papers were checked and the drug manufacturers were contacted for a list of references. Reports from drug regulatory bodies were also checked.

Study selection
Study designs of evaluations included in the review
Only double-blind randomised controlled trials (RCTs) were eligible for inclusion. Both crossover and parallel studies were included. Safety and tolerability were assessed using other clinical trials, case reports, annual reports from pharmacovigilance centres and drug regulatory authorities, and reviews.

Specific interventions included in the review
Studies assessing the effects of perhexiline were eligible for inclusion. Where stated, the dosages used in the included studies ranged from 100 to 1,200 mg/day. The control groups received placebo, prenylamine, beta-blockers (propranolol or practolol) or trimetazidine. The length of treatment ranged from 10 days to 18 weeks. The authors said that, in general, all other anti-anginal treatments, apart from nitroglycerin, were discontinued during the studies. However, one study assessed the use of perhexiline as add-on therapy to other (unspecified) conventional anti-anginal agents.

Participants included in the review
Studies on people with ischaemic heart disease were eligible for inclusion. No other details were given. There was also no information on the participants in the individual included studies, although the authors stated that they were 'generally middle aged or elderly' and suffered from angina which was inadequately controlled with other treatments. In some studies participants had myocardial infarction.

Outcomes assessed in the review
No inclusion criteria were given for the outcomes, apart from the general terms of assessing efficacy, safety and tolerability. The outcomes in the included studies were frequency of angina attacks per week, nitroglycerin consumption, physician or patient preferences, as well as objective measures such as exercise tolerance, workload or exercise-induced electrocardiograph changes. The authors also reported on the relationship between dosage and efficacy. Tolerability and adverse effects were discussed, as was information on drug interactions.

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

Assessment of study quality
The authors did not state that they assessed quality.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Details of outcomes and tolerability data for each study were extracted into tables.
Methods of synthesis
How were the studies combined?
The studies were combined in a narrative, grouped according to study comparisons (i.e. versus placebo, other drug etc.). Tolerability and safety data were grouped according to study design.

How were differences between studies investigated?
The authors discussed differences between the studies in the narrative synthesis. Differences between the studies could also be seen in the tables.

Results of the review
Thirty-six RCTs (883 participants) were included in the analysis of effects: 2 parallel-group design (57 participants) and 34 crossover design (826 participants). In addition, there were 5 studies assessing dosages, 27 clinical trial reports on adverse effects, 27 case reports and drug surveillance reports, and 3 reports of drug interactions.

Perhexiline versus placebo, monotherapy (26 RCTs): most trials showed a 50% or greater reduction in angina attacks with perhexiline compared with placebo. However, in 4 trials there was no significant difference in the number of angina attacks or use of nitroglycerine. Of the 13 trials that measured objective outcomes (maximal ST segment depression, pain-free exercise tolerance, work performance and energy expenditure), 11 showed a benefit with perhexiline.

Perhexiline as add-on therapy versus placebo (1 RCT, 17 participants): a greater number of people receiving perhexiline compared with those receiving placebo reported improvements in bicycle ergometer performance (63% versus 18%, P<0.05) and anginal symptoms (65% versus 0%, P<0.005).

Perhexiline versus other anti-anginal agents: treatment with perhexiline was associated with a reduction in angina attacks and nitroglycerine usage compared with prenylamine in 5 out of 6 studies, while 2 studies showed that perhexiline is significantly more effective at reducing angina attacks and nitroglycerine use than beta-blockers. One study assessed the effects of perhexiline versus trimetazidine, but the authors stated that it was difficult to draw any conclusion from the report because of a lack of data.

Relationship between efficacy and dosage (3 trials): one study found that the response was good or very good when the majority of participants were receiving 100 to 200 mg/day. Three studies tailored doses according to plasma concentrations in the therapeutic range (150 to 600 microg/L). These concentrations are achieved with mean daily doses of less than 200 mg/day, although there is a large difference in required dosages between individuals.

Tolerability: in clinical trials up to 60% of participants reported adverse effects. The most common adverse effects were headache, dizziness, nausea and vomiting. Less common effects were diarrhoea, lethargy insomnia, tremor and loss of libido. Symptoms usually resolved without drug discontinuation. In the 1970s and 1980s, long-term treatment was associated with infrequent but serious adverse effects (neurological, hepatic toxicity, renal impairment, loss of weight and hypoglycaemia). In drug monitoring data perhexiline has been implicated in liver damage, neurological reactions and deaths. However the authors said that the majority of these reports were prior to 1985.

Drug interactions: there were reports of possible adverse interactions with selective serotonin re-uptake inhibitors and oral anticoagulants (warfarin or phenindione).

Authors' conclusions
Despite a lack of well-designed trials, there is consistency in data suggesting that perhexiline, when used alone, is more effective than placebo for angina. It also gives some additional relief to those taking conventional anti-angina therapy. There is insufficient evidence on the effects of low dosages (100 to 200 mg/day). Evidence suggests that adverse effects can be minimised by keeping plasma perhexiline concentrations within a therapeutic range of 150 to 600 microg/L.

CRD commentary
The aims of this review were not fully stated in that inclusion criteria were not given for the participants and outcomes.
The search seemed comprehensive and the authors made attempts to identify studies that might not have been available from major databases. The methods of the review (study selection, data extraction) were not described; bias may be introduced into the review at these stages. No details of any quality assessment were given. In addition, there was little information on the participants in the included studies, and it may therefore be difficult to generalise from the results of this review.

The authors chose to synthesis the results in a narrative and grouped the studies appropriately for this. However, as part of the narrative synthesis, they used a simple vote counting approach to combine information from the studies. It would have been interesting to see a formal pooled analysis of those placebo-controlled studies that assessed similar outcomes. The authors also acknowledged that the included studies were small and short term. In view of this, and the comments above, the authors’ conclusions should be treated with caution.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice. Research: The authors suggested that further studies to assess the effects of perhexiline should be performed.

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