Pentoxifylline for heart failure: a systematic review
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CRD summary
This review assessed the effectiveness of adding pentoxifylline to standard treatment for heart failure. The authors concluded that pentoxifylline may improve cardiac function and mortality, but there was insufficient evidence to draw firm conclusions and further research is required. The authors' cautious conclusions correctly reflect the limitations of the evidence.

Authors' objectives
To assess the effectiveness of adding pentoxifylline to standard treatment for heart failure.

Searching
MEDLINE (from inception to November 2004) and the Cochrane Controlled Trials Register (Issue 4, 2004) were searched; the search terms were not reported. The reference lists of studies of pentoxifylline were checked.

Study selection
Randomised controlled trials (RCTs) were eligible for inclusion. The sample sizes in the included studies ranged from 18 to 49.

Specific interventions included in the review
Studies that compared pentoxifylline with placebo were eligible for inclusion. The included studies used pentoxifylline 400 mg three times daily for between 1 and 6 months. Co-interventions included digoxin, angiotensin-converting enzyme inhibitors, carvedilol, diuretics, spironolactone and beta-blockers. All of the studies were conducted by the same group of researchers in South Africa.

Participants included in the review
Studies of patients of any age with a diagnosis of heart failure were eligible for inclusion. The included studies were in patients with heart failure due to idiopathic dilated cardiomyopathy (New York Heart Association, NYHA, class II to IV) and ischaemic cardiomyopathy (NYHA class I to IV). All of the studies were in patients of black African descent.

Outcomes assessed in the review
The review assessed the NYHA functional class, left ventricular ejection fraction (LVEF), frequency of hospitalisation and all-cause mortality.

How were decisions on the relevance of primary studies made?
Two reviewers independently conducted searches and identified potentially relevant studies. No other details were reported.

Assessment of study quality
The studies were assessed and scored using a 5-point scale for adequacy of randomisation method, blinding, and description of withdrawals and drop-outs. The studies were also assessed for allocation concealment and use of intention-to-treat analysis. Two reviewers independently assessed validity.

Data extraction
Two reviewers independently extracted the data into a data extraction form.
Methods of synthesis
How were the studies combined?
Clinical heterogeneity between the studies and differences in the reporting of results prohibited a meta-analysis. The studies were grouped by outcome and combined in a narrative.

How were differences between studies investigated?
Clinical heterogeneity and differences in the reporting of outcomes were assessed.

Results of the review
Four double-blind RCTs (n=144) were included. These were reported in five publications.

The studies were generally of a good quality (validity score 3 to 5). Two RCTs reported adequate methods of randomisation. None of the studies reported methods used to ensure blinding (although they were reported as double-blind studies). Two RCTs reported losses to follow-up, but only one reported the use of intention-to-treat analysis.

Three of the four studies showed significant improvements in NYHA functional class and LVEF with pentoxifylline in comparison with placebo. Improvements were shown for patients with all classes of NYHA heart failure and for patients with ischaemic and idiopathic dilated cardiomyopathy.

All four studies showed a trend towards reduced mortality with pentoxifylline in comparison with placebo, but none of the studies reported a statistically significant difference.

None of the studies assessed hospitalisation.

Authors' conclusions
Pentoxifylline may improve NYHA functional class, LVEF and mortality in patients with heart failure, but there was insufficient evidence to draw firm conclusions. Further research is required.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Limiting the search to two databases might have resulted in the omission of other relevant studies. Some attempts were made to minimise publication bias, but it was unclear whether any language limitations had been applied. Methods were used to minimise bias in the validity assessment and data extraction stages, but the methods used to select studies were not reported in full. Validity was assessed using established criteria and the results were reported. Given the differences between studies, a narrative synthesis was appropriate. The authors highlighted the overlap between two of the included reports but, since the studies were all conducted by the same group of researchers, further overlap is possible and the rigour of attempts made to examine this was not clear. In addition, since all studies were small and conducted in patients with similar ethnicity, the results may not generalise to other populations. The limitations of the evidence are reflected in the authors' cautious conclusions and the need for further research was supported.

Implications of the review for practice and research
Practice: The authors stated that there is currently insufficient evidence to support the routine use of pentoxifylline in patients with heart failure.

Research: The authors stated that a large multicentre RCT is required to assess the effects of pentoxifylline on mortality and hospitalisation. Patients with heart failure of varying aetiology and severity should be included.

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