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Naftidrofuryl for intermittent claudication: meta-analysis based on individual patient data

T De Backer,^{1,2} R Vander Stichele,¹ P Leheret,³ L Van Bortel^{1,2}

EDITORIAL by Karthikeyan and Eikelboom

¹Heymans Institute of Pharmacology, Ghent University, Ghent, Belgium

²Department of Cardiovascular Disease, University Hospital Ghent, Belgium

³Department of Statistics FUCAM, Leuven Academy, Mons, Belgium

Correspondence to: T De Backer tine.debacker@Ugent.be

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STUDY QUESTION What is the efficacy and safety of oral naftidrofuryl, a specific vasoactive drug, compared with placebo in improving walking distance in patients with intermittent claudication?

SUMMARY ANSWER Oral naftidrofuryl has a clinically meaningful but moderate efficacy for improving walking distance in patients with intermittent claudication. Its safety profile in oral use is acceptable (only higher prevalence of mainly mild gastric discomfort compared with placebo). Head to head comparison of naftidrofuryl with other products used to treat intermittent claudication is the next stage. In the future, meta-analyses such as ours would be greatly aided by the establishment of, in addition to registries of randomised controlled trials, repositories of data from drug trials available for independent patient data analysis (with due consideration of patient privacy).

Selection criteria for studies

We searched Medline, International Pharmaceutical Abstracts, Embase, Science Citation Index, and the Cochrane trial registers; checked reference lists of retrieved articles; and approached authors and the manufacturer of naftidrofuryl for additional trial information and individual patient data. Our selection criteria were double blind, randomised controlled trials performed in patients with intermittent claudication receiving oral naftidrofuryl or placebo and with pain-free walking distance as the primary outcome.

We collected individual patient data from electronic data or from case report forms and checked them for data integrity. All randomised patients were analysed on the basis of intention to treat. Treatment efficacy was assessed by the ratio of the geometric mean of relative improvement in the pain-free walking distance for naftidrofuryl compared with placebo. For responder analysis, therapeutic success was defined as an improvement in walking distance of at least 50%. We assessed the safety of oral naftidrofuryl by reviewing the reports of adverse drug reactions in the selected trials, by retrieving published case reports from the literature, and by analysing the latest safety update report from the manufacturer of naftidrofuryl.

Primary outcome(s)

The primary outcome was pain-free walking distance, defined as the distance walked (in metres) during a standardised exercise test before the start of leg pain.

Main results and role of chance

The total number of randomised patients was 1266 (1083 in the main analysis). The ratio of relative

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	Difference for naftidrofuryl v placebo (95% CI)
Ratio of relative improvement in walking distance from baseline value	
Pain-free walking distance	1.37 (1.27 to 1.49)
Maximal walking distance	1.40 (1.19 to 1.63)
Responder analysis (improvement in walking distance of ≥50%)	
Response rate	22.3% (17.1% to 27.6%)
Number needed to treat over 6 months	4.48 (3.62 to 5.85)
Relative benefit	1.75 (1.50 to 2.03)
Odds ratio	2.65 (2.10 to 3.37)

improvement in pain-free walking distance for naftidrofuryl compared with placebo was 1.37 (95% confidence interval 1.27 to 1.49, $P < 0.001$). The difference in responder rate was 22.3% (17.1% to 27.6%), and the number needed to treat for symptom relief during six months of treatment was 4.48 (3.62 to 5.85).

Bias, confounding, and other reasons for caution

The question remains whether the data on which we based our meta-analysis can be trusted. We were dependent on the goodwill of Merck Darmstadt, the marketing authorisation holder for naftidrofuryl, for access to the data of studies, mostly funded by the company. We found references and full text of identified studies in the medical literature, but for the individual patient data we had to rely on the permission of Merck, as data were not readily available from the principal investigators. Some studies date from before the rigorous implementation of Good Clinical Practice.

Our meta-analysis was entirely paid for by internal funds from our university, and not by the drug manufacturer, as directed by the Cochrane Collaboration. Merck provided the data without preliminary conditions. The data were subjected to rigorous data integrity checks. Successful comparison of the data in our meta-analysis database with published results provided reassurance in this regard.

Study funding/potential competing interests

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