

Naftidrofuryl

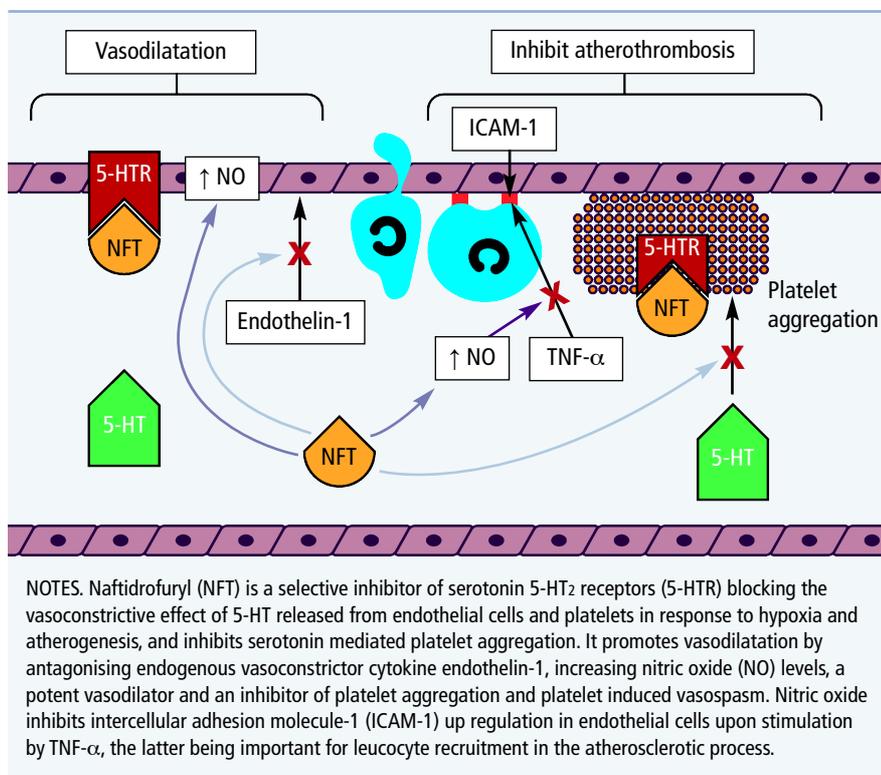


Figure 1. The pharmacological action of naftidrofuryl

Introduction

Peripheral arterial disease (PAD), whether symptomatic or not, is prevalent in about 12% of adults in the Western world.¹ Medical treatment is aimed at reducing cardiovascular morbidity and mortality, symptomatic relief and improving quality of life. PAD develops as a consequence of atherosclerosis with superimposed thrombosis. The pain in intermittent claudication results from inadequate oxygenation of lower limb muscles due to impaired blood supply. Naftidrofuryl is a vasodilator that has been used in the symptomatic treatment of intermittent claudication in Europe for more than 30 years. During recent years it has regained prominence with the emergence of more evidence of its clinical effectiveness, resulting in it being recommended for use in PAD in the UK by NICE and the Scottish Intercollegiate Guidelines Network.

Pharmacology

Figure 1 outlines the pharmacological action of naftidrofuryl which is

pharmacologically active as an oxalate salt. The precise mechanism is complex and not fully understood. It appears to exert its effect in a number of different ways. It inhibits mediators promoting atherothrombosis and improves oxygen supply to leg muscles.

Naftidrofuryl is a selective inhibitor of serotonin 5-HT₂ receptors blocking the vasoconstrictive effect of 5-HT released from endothelial cells and platelets in response to hypoxia and atherogenesis, and inhibits serotonin mediated platelet aggregation. It appears to promote vasodilatation by antagonising endogenous vasoconstrictor cytokine endothelin-1. It has been shown to increase nitric oxide levels, a potent vasodilator and an inhibitor of platelet aggregation and platelet induced vasospasm, in the endothelial milieu. Additionally, nitric oxide inhibits intercellular adhesion molecule-1 (ICAM-1) up regulation in endothelial cells upon stimulation by TNF- α , the latter being important for leucocyte recruitment in the atherosclerotic process.

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Finally, naftidrofuryl also appears to improve aerobic metabolism in the blood vessel wall and has been shown to increase flexibility and reduce aggregability of erythrocytes enhancing blood flow to the tissues.

Trials of safety and efficacy

Efficacy

Several small ($n < 50$) to medium-scale ($n = 100$ – 200) randomised placebo-controlled trials of naftidrofuryl have been carried out from 1978–2001 in patients with PAD. Among the trials that were conforming with the current European guidelines on clinical trial methodology in PAD is the Naftidrofuryl Clinical Ischemia Study (NCIS).² This was a randomised, double-blinded, parallel-group and placebo-controlled clinical trial carried out in 196 patients recruited from five hospitals in Paris but who were assessed in a single centre. The patients were men and women aged 35–85 years who were at Fontaine Stage II PAD for at least six months. The primary endpoints were the change from baseline in pain-free walking distance (PFWD) and maximum walking distance (MWD) measured on a treadmill. Ankle brachial index (ABI) was measured as a secondary outcome. Patients were randomised to receive naftidrofuryl 200mg three times a day or matching placebo for six months. Results were reported as geometric means to reduce the impact of normal variation in walking distance and the effect of extreme values. In the intention-to-treat analysis, PFWD was increased by 91.8% (158.2m) in the naftidrofuryl group compared to an increase of 16.8% (29.9m) in the placebo group ($p < 0.001$). The increase in MWD was 82.7% (158.7m) and 13.9% (28.1m) for the naftidrofuryl and placebo groups, respectively ($p < 0.001$). There was no significant difference in change in ABI between the groups.

A recent Cochrane systematic review using individual patient data from six trials (1083 patients) looked at the effect of oral naftidrofuryl (200mg three times a day) compared with placebo in patients with intermittent claudication (Fontaine Stage II).³ The main endpoint was the relative improvement (RI) in geometric mean of PFWD ($RI = WDr/WDo$,

where WDr and WDo are designated as final and baseline PFWD values, respectively). The treatment effect was measured by the ratio $RI_{\text{naftidrofuryl}}/RI_{\text{placebo}}$. A further clinical primary endpoint assessed in the systematic review was the responder analysis. A patient was considered as a responder to therapy when the PFWD improved by at least 50% from baseline. The ratio of $RI_{\text{naftidrofuryl}}/RI_{\text{placebo}}$ MWD is measured as a secondary outcome. The ratio of the relative improvement in PFWD (naftidrofuryl compared with placebo) was 1.37 (95% CI 1.27–1.49; $p < 0.001$). The corresponding figure for the ratio of relative improvement in MWD was 1.40 (95% CI 1.19–1.63). The responder analysis for PFWD identified 30.2% and 54.7% responders for placebo and naftidrofuryl, respectively. The absolute difference in responder rate was 22.3% (95% CI 17.1–27.6). The number needed to treat was 4.48 (95% CI 3.62–5.85).

Safety

In the NCIS trial there were no differences between the naftidrofuryl or placebo groups in terms of number of serious or non-serious adverse events. In the Cochrane systematic review there was no significant difference between both groups in relation to moderately severe adverse events. However, the proportion of cardiovascular adverse events was slightly higher in the placebo group. In the naftidrofuryl group the proportion of gastric disorders was higher with a risk difference of 2.85% (95% CI 0.78–4.91%) compared with placebo. The reported gastric adverse events were minor side effects such as nausea, epigastric pain, oesophagitis and diarrhoea.

Specific evidence for use in diabetes

Patients with type 1 diabetes mellitus were excluded from the NCIS trial and other studies included in the Cochrane review. Twenty percent of the patients in the NCIS trial had type 2 diabetes and they were stratified between treatment groups. There was no significant difference in results in this study between those with or without diabetes. The whole database of the Cochrane individual

Key points

- Naftidrofuryl oxalate is a vasodilator that exerts its effects mainly via selective inhibition of 5-HT₂ receptors on vascular endothelium and platelets
- It is found to be efficacious in improving PFWD, MWD and HR-QOL when used for six months or more in the treatment of intermittent claudication due to peripheral vascular disease
- There was no difference in therapeutic efficacy of naftidrofuryl between patients with type 2 diabetes and those without

patient data meta-analysis included 13.4% patients with type 2 diabetes.

Discussion

Peripheral vascular disease is a common condition with evidence that treatment may help symptoms, and this is reflected in studies comparing it with placebo in improving health related quality of life (HR-QOL).

There are no head-to-head comparisons between naftidrofuryl and other vasodilator medicines. However, a meta-analysis conducted by NICE revealed that naftidrofuryl and cilostazol are the only vasoactive medicines having clinically significant efficacy in the treatment of PAD, and the former is more effective than the latter.⁴

A cost-effectiveness analysis conducted by NICE revealed naftidrofuryl oxalate is cost effective to be used in the UK NHS, as opposed to cilostazol and pentoxifylline that failed to reach the cost-effectiveness threshold.⁴

In conclusion, naftidrofuryl may have a use in providing symptomatic benefit in patients with peripheral vascular disease including those with diabetes, but as borne out by the clinical evidence there may be those who respond and those who do not, so assessment of clinical response after a period of treatment (six months) is recommended.

Declaration of interests

There are no conflicts of interest declared.

References

References are available in *Practical Diabetes* online at www.practicaldiabetes.com.

References

1. Hiatt WR, *et al.* Effect of diagnostic criteria on the prevalence of peripheral arterial disease. The San Luis Valley Diabetes Study. *Circulation* 1995; 91(5):1472–9.
2. Kieffer E, *et al.* A new study demonstrates the efficacy of naftidrofuryl in the treatment of intermittent claudication. Findings of the Naftidrofuryl Clinical Ischemia Study (NCIS). *Int Angiol* 2001; 20(1):58–65.
3. De Backer TLM, *et al.* Naftidrofuryl for intermittent claudication. *Cochrane Database Syst Rev* 2012; 12:CD001368.
4. National Institute for Health and Care Excellence. *Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease. TA223*. London: National Institute for Health and Care Excellence, 2011.