Br. J. Surg. Vol. 67 (1980) 349–351 *Printed in Great Britain*

The effect of naftidrofuryl (Praxilene) on intermittent claudication

KENNETH J. WATERS, ALAN D. CRAXFORD AND JOHN CHAMBERLAIN*

SUMMARY

In a randomized double-blind controlled trial the effect of naftidrofuryl (Praxilene) 200 mg t.d.s., taken for 6 months, was compared with placebo in intermittent claudication. Whilst there was a significant subjective improvement regardless of age or treatment, patients over 60 on naftidrofuryl experienced a more rapid symptomatic relief than other patients. At six months this age group showed a significant improvement over the placebo group. There was no significant objective evidence of improvement.

INTERMITTENT claudication is a very common and disabling symptom. Although reconstructive surgery may be very effective in certain patients, the general condition of other patients or the site of the arterial lesion may preclude reconstruction. Drug therapy has been disappointing. Appropriate drugs may improve cardiac output when claudication is exacerbated by a low output state or when it is associated with anaemia, polycythaemia or hyperfibrinogenaemia (1, 2). There is, however, no drug which acts directly on the atherosclerotic artery to improve flow. Vasodilator drugs have been used but shown to be of doubtful benefit (3) or even detrimental (4) to the ischaemic limb.

Naftidrofuryl (Praxilene) is an acid oxalate of β-naphthyl-l-β tetrahydrofuryl diethanolamine isobutyrate and is said to be vasoactive. It is known to have a local anaesthetic action (5) and when given intravenously may have a sympathectomy-like effect (6, 7). It has also been shown to act at tissue level (8, 9), improving tissue oxygenation, to increase ATP levels and reduce lactic acid levels thereby improving claudication symptoms. The drug may be administered orally; the manufacturers originally suggested a dose of one capsule (100 mg) t.d.s. In a small double-blind trial, Ruckley et al. (10) found no overall difference between naftidrofuryl and placebo at this dose. This paper reports the results of a trial of naftidrofuryl at a dose of 200 mg t.d.s. in patients with intermittent claudication.

Patients and methods

Non-diabetic patients with moderate claudication and in whom surgery was not indicated were admitted to the trial. There were 69 patients, 59 males and 10 females, between the ages of 48 and 78. Thirteen patients left the trial before completing the 6 months for a variety of reasons discussed below, leaving 56 patients with 82 symptomatic limbs.

The trial was double-blind. Each patient was given supplies of pink capsules in a numbered bottle, with instructions to take two capsules t.d.s. Each number signified naftidrofuryl or placebo and had been allocated randomly. The code was kept in a sealed envelope.

Progress was assessed subjectively and objectively at 2 months, 4 months and 6 months. The patient was given an initial subjective score of 3 for a symptomatic limb and 6 for an asymptomatic limb. If one limb was notably less affected than the other an appropriate score of between 3 and 6 was given. On subsequent visits the score was raised, lowered or left unchanged according to improvement or otherwise. The objective methods of assessment employed Doppler ultrasound, as described by Yao et al. (11, 12) and Chamberlain et al. (13). Each patient's resting ankle/brachial pressure (normally > 1) was measured with sphygmomanometer cuffs around the calf and arm, and then the patient was exercised on a treadmill at a speed of 3·5 kph for 5 min or until claudication ensued. The ankle pressure was then measured at 1-min intervals for 15 min and the patient given a score from 4 (normal response) to 0 (resting value not attained after 15 min) according to the shape of the pressure curve (*Fig.* 1).

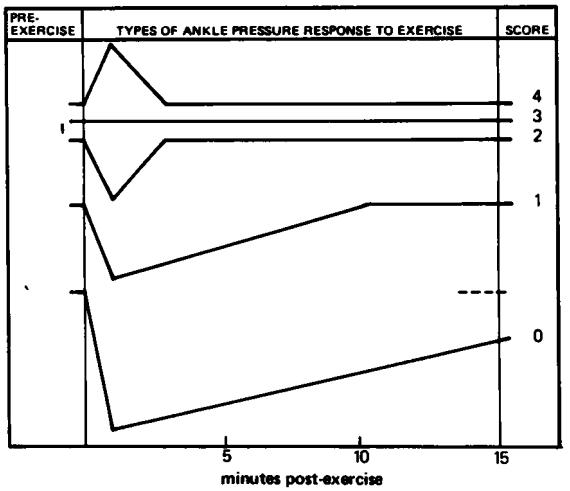

Fig. 1. Types of ankle pressure response to exercise with scoring (4 = normal, 0 = severely ischaemic).

In view of the discrete nature of scoring, the statistical significance of subjective changes and exercise response changes was assessed with non-parametric statistics. Changes in each group of limbs were assessed with the Mann–Whitney U test. Changes in resting pressure index were evaluated both non-parametrically as above and parametrically with *t* tests. When comparing the distribution of limbs that had improved, remained static or deteriorated between each group of patients χ^2 tests and Fisher's exact test were used appropriately.

Results

Thirteen patients did not complete the 6 months: 10 of these were subsequently found to be taking the placebo, 4 of whom sustained myocardial infarctions, 3 required reconstructive vascular surgery, 1 developed a hepatic malignancy and 1 patient stopped taking the capsules after one day due to diarrhoea and vomiting. Of the 3 who were taking naftidrofuryl, 1 developed a diverticular abscess and the other 2 either defaulted or did not wish to continue in the trial.

* Department of Surgery, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP.
Correspondence to: J. Chamberlain, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BR.

Table I: SUBJECTIVE IMPROVEMENT DURING EACH 2-MONTH PERIOD AND IN THE FULL 6 MONTHS EXPRESSED AS *P* VALUE (WILCOXON MATCHED PAIRS TEST)

Group	No. of limbs	Improvement 0–2	2–4	4–6	0–6
Drug ⩽60 yr	23	0·075	0·043	0·068	0·004
Placebo ⩽60 yr	15	0·059	0·043	0·059	0·004
Drug >60 yr	19	0·005	0·043	0·012	0·001
Placebo >60 yr	25	0·522	0·308	0·078	0·019

Table II: SIGNIFICANCE OF TREATMENT BY SUBJECTIVE EVALUATION COMPARING EACH GROUP INITIALLY AND AT 6 MONTHS (MANN–WHITNEY U TEST)

Treatment groups compared	Initial	6 mth
Drug ⩽60 yr *v.* Placebo ⩽60 yr	n.s.	n.s.
Drug >60 yr *v.* Placebo >60 yr	n.s.	$P<0·05$
Drug ⩽60 yr *v.* Drug >60 yr	n.s.	$P<0·05$
Placebo ⩽ 60 yr *v.* Placebo >60 yr	n.s.	n.s.
Drug >60 yr *v.* Placebo ⩽60 yr	n.s.	n.s.
Drug <60 yr *v.* Placebo >60 yr	n.s.	n.s.

Fifty-six patients continued in the trial. Five complained of indigestion (four taking naftidrofuryl), 4 complained of headaches (3 taking naftidrofuryl) and 1 patient developed a transient skin rash while taking naftidrofuryl.

Subjectively there was a significant improvement in each group of patients over the 6-month trial period. There was no overall difference between those taking naftidrofuryl and placebo, but when analysed by age, differences became apparent (*Table I*). There was an early and significantly consistent improvement in those patients over 60 on naftidrofuryl. At 6 months this was greater than the improvement attained on placebo. This did not occur in the younger age group. The older patients on naftidrofuryl improved significantly over the younger patients on naftidrofuryl but not over the younger placebo-treated patients (*Table II*). Despite this qualitative improvement there was no significant difference in the distribution of numbers of limbs improved or otherwise between each group. There were no significant changes in resting pressure index or exercise response in any group.

Discussion

The results of this trial demonstrate that whilst the symptoms of intermittent claudication may improve spontaneously, the administration of oral naftidrofuryl at a dose of 200 mg t.d.s. can enhance this improvement in patients over 60 years of age. This would not have become apparent if the naftidrofuryl-treated group had been compared against placebo regardless of age, as the findings then were similar to those of Ruckley et al. (10). The latter authors found no significant difference between naftidrofuryl and placebo, although they used a dose of 100 mg naftidrofuryl t.d.s. The difference in response according to age group is probably related to the differing natural history of peripheral vascular disease. Older patients tend to remain relatively static compared with the spontaneous improvement often seen in the younger age group. A good placebo response may therefore be expected in the younger group, which may render impossible the assessment of the drug effect. Conversely, the static nature of the older claudicant may expose the benefit of the drug therapy. At 6 months there was a significant symptomatic improvement of the over-60 group on naftidrofuryl over the younger group on naftidrofuryl and therefore the drug may possibly alter the older claudicant's appreciation of his symptoms.

The absence of objective improvement either in resting pressure index or ankle pressure response to exercise denotes that any benefit was unlikely to be due to the development of a collateral circulation. However, it has been shown that claudicants undergoing physical training are able to develop an increased exercise capacity without a commensurate increase in blood flow (14). They were found to have a lowered popliteal venous oxygen saturation and a lowered lactate release during exercise. This could be due to an increased oxygen extraction by the leg muscles during exercise, a capacity which naftidrofuryl could possibly augment.

It is concluded that oral naftidrofuryl at a dose of 200 mg t.d.s. may be of some benefit to patients over 60 years of age with intermittent claudication. This concurs with a preliminary report by Clyne et al. (15). The dose may be important.

Acknowledgements

We wish to thank Lipha Pharmaceuticals UK Ltd for their kind cooperation with this trial in supplying naftidrofuryl and placebo. We also thank Miss D. E. Lenaghan for typing the manuscript.

References

1. DORMANDY J. A., GUTTERIDGE J. M. C., HOPE E. et al.: Effect of clofibrate on blood viscosity in intermittent claudication. *Br. Med. J.* 1974; **4**: 259–62.
2. POSTLETHWAITE J. C. and DORMANDY J.: Results of ankle systolic pressure measurements in patients with intermittent claudication being treated with clofibrate. *Ann. Surg.* 1975; **181**: 799–808.
3. GOFFMAN J. D.: Vasodilator drugs in peripheral vascular disease. *Am. J. Hosp. Pharm.* 1975; **32**: 1276–81.
4. GILLESPIE J. A.: The case against vasodilator drugs in occlusive vascular disease of the legs. *Lancet* 1959; **2**: 995.
5. FONTAINE L., GRAND M., CHABERT J. et al.: General pharmacology of a new vasodilator substance—naftidrofuryl. *Bull. Chem. Ther.* 1968; **6**: 463–9.
6. SCHERER H. J., MACK D., MAURER P. et al.: Praxilene—a preoperative indicator in the treatment of chronic arterial insufficiency in the lower limbs by lumbar sympathectomy. *Lyon Chir.* 1973; **69**: 280–1.
7. GREENHALGH R. M. and HOARE M.: The effect of naftidrofuryl (Praxilene) on patients with ischaemic rest pain. *Abstracts of the Proceedings of the Vascular Surgery Society of Great Britain and Northern Ireland*, 1977.
8. ELERT C., NIEBEL W. and KRAUSE E.: The effect of naftidrofuryl on energy metabolism in the musculature of limbs with impaired blood flow. *Therapiewosche.* 1976; **23**: 3947–50.
9. SHAW S. W. J. and JOHNSON R. H.: The effect of naftidrofuryl on the metabolic response to exercise in man. *Acta Neurol. Scand.* 1975; **52**: 231–7.
10. RUCKLEY C. V., CALLAM M. J., FERRINGTON C. M. et al.: Naftidrofuryl for intermittent claudication—a double blind controlled trial. *Br. Med. J.* 1978; **1**: 622.
11. YAO S., HOBBS J. T. and IRVING W. T.: Ankle systolic pressure measurements in arterial disease affecting the lower extremities. *Br. J. Surg.* 1969; **56**: 676–9.
12. YAO S.: Haemodynamic studies in peripheral arterial disease. *Br. J. Surg.* 1970; **57**: 761–6.

13. CHAMBERLAIN J., HOUSLEY E. and MCPHERSON A. I. S.: The relationship between ultrasound assessment and angiography in occlusive arterial disease of the lower limb. *Br. J. Surg.* 1975; **62**: 64–7.
14. SORLIE D. and MYHRE K.: The effects of physical training in intermittent claudication. *Scand. J. Clin. Lab. Invest.* 1978; **38**: 217–22.
15. CLYNE C. A. C., GUSTAVE R. and JAMIESON C. W.: Naftidrofuryl (Praxilene) in the treatment of claudicaton. *Proceedings of the 27th International Congress of the European Society of Cardiovascular Surgeons*, 1977: 100.

Paper accepted 31 August 1979.

Statistics in *The British Journal of Surgery*

It is part of the clinical scientist's stock-in-trade to use statistical methods. In many instances, and by most readers, these can be taken on trust, but in that there is a wide variety of tests and, on occasion, disagreement amongst both amateurs and professionals on the best choice, it is always wise that authors quote the method used. It is indeed journal policy to quote methods, the reason for their choice and, in the case of clinical trials, the confidence or tolerance limits of the observed results. Delay in acceptance may occur if contributors do not include these details.