

Effects of naftidrofuryl on breathlessness and exercise tolerance in chronic bronchitis

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ABSTRACT Naftidrofuryl enhances oxidative phosphorylation and might therefore be expected to improve exercise tolerance and breathlessness in advanced chronic bronchitis. This hypothesis was tested in a four-week placebo-controlled trial in 11 bronchitic patients. Seven patients completed the study. There was no evidence of any benefit from naftidrofuryl either subjectively or after a 12-minute walking test.

Some patients with chronic airflow limitation have distressing breathlessness and severely limited exercise tolerance despite therapeutic efforts to improve lung function. Attention has therefore been turned to alternative methods of relieving these symptoms. Physical training may improve exercise tolerance¹ in chronic bronchitics, and portable oxygen also improves exercise tolerance and relieves breathlessness in "pink puffers."² Promethazine may also be of marginal benefit.³ Reducing basal metabolic rate and thus oxygen requirements by inducing hypothyroidism might be expected to leave more oxygen available for exercise, but in a controlled study using carbimazole no improvement in exercise tolerance was achieved.⁴

Naftidrofuryl (currently in use for the treatment of peripheral vascular disease) has novel effects on cellular metabolism. In mice the drug produces raised concentrations of cerebral adenosine triphosphate, phosphocreatine, and glucose, reduced lactate concentrations, and protection against the metabolic effect of ischaemia.⁵ Similar effects have been shown in the affected limbs of patients with peripheral vascular disease,⁶ and lowered lactate:pyruvate ratios after exercise in healthy volunteers given naftidrofuryl indirectly confirm that the drug enhances tissue oxidative metabolism.⁷ Because of these properties we thought that a study of the effects of naftidrofuryl on exercise tolerance and breathlessness in patients with severe chronic airflow limitation was warranted.

Methods

Eleven patients (10 men) with stable chronic obstructive bronchitis were studied. Their mean age was 60 years (range 56-65). All had disabling breathlessness (MRC grades 3 and 4) and severe fixed airflow limitation (mean forced expiratory volume in one second (FEV₁) 0.80 l, range 0.45-1.20 l; mean forced vital capacity (FVC) 2.3 l, range 1.7-3.2).

Patients received naftidrofuryl 200 mg thrice daily or placebo, each given for two weeks in a randomised double-blind crossover study. They continued their usual medications throughout. All gave informed consent. Exercise tolerance was assessed by measuring the 12-minute walking distance in an enclosed hospital corridor.⁸ Each patient completed four tests, two before entry to the study, the second of which was taken as the baseline, and one after each treatment period. Each test was performed at the same time of day and prior consumption of cigarettes and medication was standardised. After each test a rating of the perceived exercise was scored by the patient.⁹ Lung function (FEV₁ and FVC) was assessed on each test day. Throughout the study period patients made a daily assessment of breathlessness on a 10-cm visual analogue scale. For each patient the midpoint of the scale represented his usual degree of breathlessness, and improvement and deterioration were shown by positive (up to +5 cm) and negative (up to -5 cm) deviations. Statistical analysis of results was by analysis of variance.

Results

Four patients were withdrawn—two with exacerbations of bronchitis, one with intercurrent infective

Lung function and exercise tolerance during treatment with naftidrofuryl and placebo in seven patients with chronic bronchitis

Naftidrofuryl

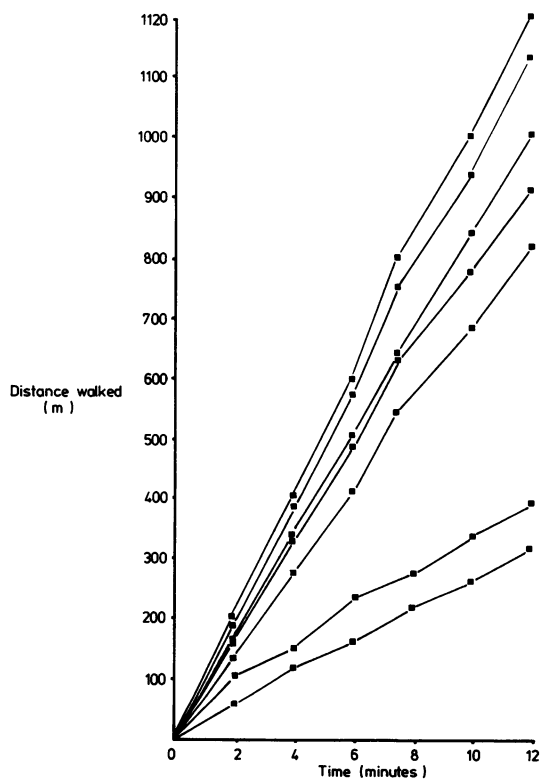
Patient	Before treatment				After treatment				
	FEV ₁	FVC	12-MD	RPE	FEV ₁	FVC	12-MD	RPE	VAS
1	1.1	2.9	1172	20	0.95	2.75	1107	16	-1.5
2	0.85	2.5	1008	15	0.9	2.8	1019	16	+0.34
3	0.5	1.3	320	17	0.5	1.15	371	17	-1.99
4	0.95	2.7	824	17	0.95	3.05	840	16	+0.16
5	1.1	3.2	1231	15	1.1	3.2	1242	13	-0.17
6	1.0	2.6	1003	17	0.9	2.4	1004	16	+0.15
7	0.55	1.75	374	17	0.45	1.75	455	17	+2.18
Mean	0.86	2.42	847	16.86	0.82	2.44	862	15.85	-0.12

gastroenteritis, and one with epigastric and chest pain that he developed while taking the active preparation. Of the seven patients who completed the study, three received naftidrofuryl and four the placebo during the first treatment period. Results are shown in the table. Analysis of variance showed no significant effect of the drug for any of the variables measured.

Discussion

Naftidrofuryl produced no improvement in exercise tolerance or decrease in breathlessness in our patients. If an increase in intracellular energy-rich compounds did occur with naftidrofuryl, possibly it was insufficient to produce a noticeable effect, or these compounds were rapidly consumed at the onset of exercise. In anticipation of the latter possibility distance walked was measured at two-minute intervals during the exercise tests. No fall-off in the two-minute walking distance was seen during the 12-minute test, which suggests that not even brief benefit, sufficient for short-lived exercise, was obtained. Indeed, the rate of walking remained constant through the whole test for each patient on each occasion (fig), confirming the finding of Butland and colleagues¹⁰ and suggesting that a shorter test (for example, six minutes) would be as valuable. A further possibility is that the vasodilator properties of naftidrofuryl,¹¹ which may extend to the pulmonary circulation and lead to ventilation and perfusion mismatch and subsequent hypoxaemia, may have negated any beneficial metabolic effects of the drug. This possibility has not been investigated in the present study.

The experimental evidence suggests that the intracellular effects of naftidrofuryl occur rapidly.⁷ It is therefore unlikely that our two-week treatment was too short to show an effect. Equally we feel that



Distance walked (in metres) at two-minute intervals during the 12-minute walking test in seven bronchiitic patients (before treatment).

a prolonged carry-over effect was unlikely to have influenced our results.

In conclusion, this study shows no benefit from naftidrofuryl in the palliation of symptoms in severe chronic airflow limitation.

Placebo

Patient	Before treatment				After treatment				
	FEV ₁	FVC	12-MD	RPE	FEV ₁	FVC	12-MD	RPE	VAS
1	1.1	2.9	1133	20	1.1	2.9	1172	20	+0.25
2	0.8	2.2	922	17	0.85	2.5	1008	15	+0.22
3	0.5	1.15	371	17	0.55	1.35	445	18	-2.32
4	0.95	3.05	840	16	0.9	2.7	813	17	-0.19
5	1.2	3.1	1203	15	1.1	3.2	1231	15	-0.01
6	0.9	2.4	1004	16	1.0	2.8	966	17	-0.09
7	0.55	1.55	389	20	0.55	1.75	455	17	+0.36
Mean	0.86	2.34	837	17.3	0.86	2.46	870	17	-0.25

FEV₁ = forced expiratory volume in 1 second (l BTPS); FVC = forced vital capacity (l BTPS); 12-MD = distance (m) walked in 12 minutes; RPE = rating of perceived exercise (score 0-20); VAS = mean daily score of breathlessness during the second week of each treatment period scored on a 10-cm visual analogue scale.

We are grateful to Mr T Brown of Lipha Pharmaceuticals for supplies of naftidrofuryl and placebo and for assistance with the statistical analysis. We also wish to thank Mrs M Jervis for secretarial assistance.

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