

of hypercoagulation even in patients with a relatively slender family history. Plasma or serum samples may be conveniently tested by immunodiffusion techniques, though there may be false-negative results unless a clot inhibition assay is used as well. It is reasonable to start prophylactic warfarin anticoagulation of the clinically affected. The use of heparin is to be avoided as its main effect follows binding to the antithrombin III globulin.¹ The treatment of the asymptomatic individual is undecided. Judgment can be based on the presence of further risk factors, including age, obesity, varicose veins, high oestrogen concentrations, and hypertriglyceridaemia.

The incidence of antithrombin deficiency in Norway and Massachusetts has been estimated to be about 1 in 2000.⁵ In Britain several families have been recognised, though few reported, but many more probably remain to be discovered.

We thank Dr P A Harrison and Dr H S Marwick for their help in tracing and obtaining samples from this family.

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(Accepted 25 November 1977)

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Naftidrofuryl for intermittent claudication: a double-blind controlled trial

Intermittent claudication is the commonest symptom of an increasingly common disorder: obliterative arterial disease affecting the legs. Hitherto, despite the wide pharmaceutical range offered, there has been little medical treatment of proved value to prescribe and, in particular, vasodilator drugs have proved disappointing. This paper describes a double-blind controlled trial of naftidrofuryl (Praxilene), a new drug that is believed to facilitate oxygen exchange and enhance metabolism in ischaemic tissues.

Patients, methods, and results

Consecutive patients attending a peripheral vascular clinic with stable claudication were included. Once informed consent had been obtained the patient was issued with capsules in a coded container, maintaining a double-blind design. The treatment group received naftidrofuryl 100 mg thrice daily for three months; the controls received an inert placebo capsule of identical appearance. Assessment was based both on subjective and objective criteria. The patient was asked to take regular exercise and to note any improvement or deterioration. No specific instructions on smoking or diet were given during the period of observation. Clinical severity was defined according to the reported onset of claudication at normal walking pace on the level: less than 100 yards—severe; 100-200 yards—moderate; more than 200 yards—mild. A standard exercise test was performed before and one month and three months after starting treatment. Both legs were tested simultaneously by Doppler ultrasound ankle pressure ratios and gastrocnemius ^{99m}Tc clearance.¹⁻³

One patient who failed to attend after initial assessment was excluded. Fifty patients (25 on naftidrofuryl and 25 controls) were included. One failed to attend for the final test but was included for analysis at one month. The groups were similar in age and sex distribution. The initial severity of disease, judged clinically, showed some difference between the two groups. Among the naftidrofuryl-treated patients 15 had mild, three had moderate, and seven had severe disease. The corresponding numbers in the control group were 9, 6, and 10. Nevertheless, the level of initial clinical severity had no appreciable effect on subsequent changes in the levels of other variables. Most patients in both groups reported improvement, with a similar pattern of response in each group (see table). Few patients showed a change in clinical sev-

Subjective response in the two groups

	Worse	No change	Slight improvement	Improvement
Naftidrofuryl	2	7	3	13
Control	2	9	1	13

erity: seven improved (two on naftidrofuryl, five controls) and two showed an increase in clinical severity (one on naftidrofuryl, one control). The following variables were examined in both legs: the onset of claudication on the treadmill, the stopping time, the resting ultrasound pressure index, the post-exercise fall in pressure, and the ^{99m}Tc clearance before, during, and after exercise. These measurements were examined in both legs. There were no statistically significant differences (at 5% level) between the treatment and control groups (Wilcoxon's rank sum test). No serious side effects were reported. Six patients treated with naftidrofuryl reported symptoms during treatment: vertigo (in two cases), nausea (two), and slight insomnia (two). One control reported epigastric pain, one indigestion, one constipation, and one headache with nausea.

Comment

The tendency for symptoms of claudication to improve during a period of observation is well known to those interested in vascular disease and probably accounts for the gross overprescribing of vasodilator or "vasoactive" drugs. This improvement occurred despite the fact that patients with apparently stable claudication were studied and that specific instructions on diet and smoking were withheld. In effect, by observing their own symptoms regularly, the patients were undertaking a programme of exercise similar to that commonly recommended for the condition.

We have been unable to show a benefit in our patients with claudication from oral naftidrofuryl. The administration of naftidrofuryl in more advanced vascular disease and by alternative routes may have different effects and requires separate study.

We are grateful for the support of Lipha UK Ltd, who also provided supplies of naftidrofuryl (Praxilene). We thank Dr Lucy Ward, Dr Margaret Bateman, and Dr John Hoyle who helped with the study.

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(Accepted 10 August 1977)

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Urinary incontinence caused by prazosin

The antihypertensive effect of prazosin is thought to result primarily from arteriolar smooth muscle relaxation and consequent peripheral vasodilatation.¹ Soon after its introduction reports² appeared of collapse due to postural hypotension ("first dose phenomenon"), suggesting an effect on the sympathetic nervous system. Recent experimental data favour the hypothesis that prazosin interferes with α -adrenoceptor function at the postsynaptic level.³ Our patient furnishes a new clinical argument for this hypothesis.

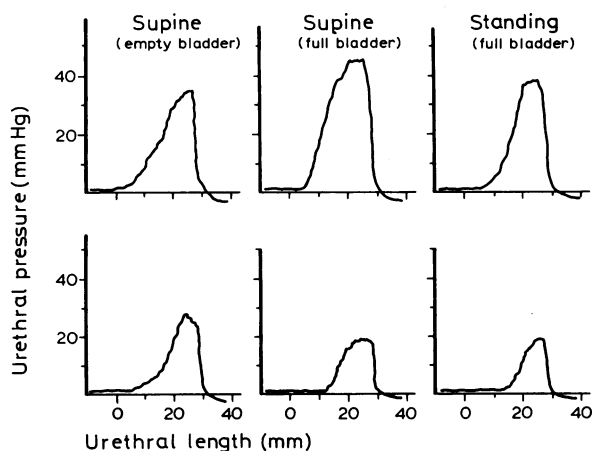
Case report

A 58-year-old woman was referred because of hypertension (200/118 mm Hg). She had experienced repeated urinary tract infections after a pyelitis

during pregnancy. A slight stress incontinence had remained after an operation for vaginal prolapse in 1967. Renal function was normal, and the intravenous urogram showed only slight pyelonephritic changes. Urinary cultures were negative. Because blood pressure control with 50 mg chlorthalidone and 300 mg metoprolol daily was insufficient prazosin was added in a dose increasing in four weeks from 1.5 to 6 mg daily. On a dose of 3 mg she developed orthostatic complaints, and she collapsed once. After four weeks she complained of complete incontinence of urine, which started one to two hours after taking prazosin. One day after prazosin withdrawal the incontinence had disappeared.

Urodynamic investigations were then performed before and during treatment with prazosin. Urethral closure pressure profiles were obtained by the catheter-withdrawal technique⁴ with an empty bladder in supine position, and with a full bladder (400 ml) supine and standing. These profiles give a measure for the maximum urethral closure pressure (maximum urethral pressure minus bladder pressure) and the functional urethral length (distance where urethral pressure exceeds bladder pressure). To exclude urinary incontinence caused by "unstable bladder" a cystometrogram with pressure/flow analysis was also performed.

In the three investigations before taking prazosin the maximum closure pressure and the functional urethral length were low-normal (see figure).



Urethral pressure profiles before (upper panel) and during (lower panel) treatment with prazosin (12 mg daily).

The cystometrogram was normal. During micturition the maximum flow rate was 38 ml/sec (normal value for women 30 ml/sec). There was a detrusor contraction to 12 mm Hg without abdominal strain during micturition. After one week of prazosin (12 mg daily) the maximum closure pressure had decreased to abnormally low values. The height of the proximal part of the pressure profile had diminished, resulting in a substantial decrease of the functional urethral length (see figure). Again, the cystometrogram was normal but the maximum flow rate was now higher (47 ml/sec), while the detrusor contraction had slightly decreased (8 mm Hg). One day after prazosin withdrawal results identical with those before treatment were obtained.

Comment

The urinary incontinence in this patient was probably caused by prazosin. Withdrawal of the drug led to immediate disappearance of the symptoms on two occasions, while reinstatement was followed by complete incontinence. The results of the urodynamic study suggest that this side effect is caused by α -adrenergic receptor blockade. The urethral pressure is determined by the tonus of the smooth muscles of the proximal, presphincteric part of the urethra that are innervated by sympathetic nerves. Administration of phentolamine, a known α -adrenergic receptor blocker, decreases the maximal urethral closure pressure and the functional urethral length. The latter decrease is caused by a pressure fall in the proximal urethra to the level of the bladder pressure.⁴ Identical changes were observed in our patient during treatment with prazosin. Although normal people show differences in profiles with empty and full bladder, we found more impressive changes with full bladder. This might be related to the pre-existing stress incontinence in our patient. This minor dysfunction could have also caused the exaggerated reaction to prazosin. Several authors mention urinary frequency and sometimes incontinence as a side effect of prazosin.⁵ In our own group three out of 30 patients treated with prazosin developed urinary incontinence. One of them had already been operated on for this problem. Apart from the reported postural hypotension and the first dose phenomenon we

found another clinical argument for the hypothesis that prazosin has α -sympatholytic activity and is not a pure smooth-muscle relaxant.

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(Accepted 10 August 1977)

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Cytomegalovirus and vasculitis

Cytomegalovirus (CMV) infection in adults causes several clinical syndromes. We report a patient with CMV infection who developed vasculitis and believe that this is the first recorded association.

Case history

A 57-year-old woman with longstanding, well-controlled diabetes was admitted to St Martin's Hospital in May 1976 for stabilisation of her disease after three weeks of ill health with an upper respiratory tract infection and itchy rash on both legs. She had had rheumatic fever in childhood. On admission her temperature was 38°C and her throat inflamed. There was one subungual splinter haemorrhage and a macular rash on both legs. Pulse was 92/min, regular; blood pressure was 120/60 mm Hg; and an ejection systolic murmur was audible at the left sternal edge. The jugular venous pressure was not raised but her ankles were oedematous. Scattered crepitations were audible in both lungs. Liver and spleen were palpable. A provisional diagnosis of bacterial endocarditis was made.

Investigations showed (normal ranges in parentheses): haemoglobin (Hb) 10.5 g/dl; white cell count $3.7 \times 10^9/l$ (39% lymphocytes, some atypical); plasma viscosity 1.85 centipoise (1.5-1.72 centipoise); Paul-Bunnell negative; urea 12.4 mmol/l (75 mg/100 ml) (2.5-6.6 mmol/l (15-40 mg/100 ml)); glucose 16.7 mmol/l (301 mg/100 ml) (3.3-5.6 mmol/l (59-101 mg/100 ml)); alkaline phosphatase 400 IU/l (21-92 IU/l); aspartate aminotransferase (SGOT) 78 IU/l (13-42 IU/l); γ -glutamyltranspeptidase 476 IU/l (<40 IU/l). Chest x-ray film and electrocardiogram were normal. Urine was sterile on culture. *Staphylococcus albus* contaminated two of six blood cultures. ASO titre was normal. Hepatitis B antigen was negative. Blood was sent for determination of viral antibodies.

Her insulin dosage was increased, and over the next 10 days two more splinter haemorrhages appeared. Her fever settled, her condition improved without antibiotics, and she was discharged. The results of viral studies available after discharge showed a diagnostic rise in CMV titre from 1/16 to 1/256 between 21 and 27 May 1976 (complement fixation tests: plate microtitre using killed CMV in human fibroblasts from Public Health Laboratory, Colindale). The titres to other viruses were insignificant.

One month later she was readmitted because of increasing fatigue and bouts of sweating. She was febrile, in congestive cardiac failure, and had several new splinter haemorrhages, while the systolic murmur persisted and her liver was tender and enlarged. Investigations showed: Hb 8.7 g/dl, white cells $9.8 \times 10^9/l$, viscosity 2.16 centipoise, urea 17.5 mmol/l (105 mg/100 ml), glucose 24.1 mmol/l (434 mg/100 ml), and SGOT 66 IU/l. A chest x-ray film now showed cardiac enlargement and shadowing in the right lower lobe. Fourteen blood cultures were sterile. Routine autoantibody screen was negative. After admission she developed aching pains in the arms with exquisite tenderness on palpation. Muscle biopsy was performed and prednisone 60 mg daily started for her presumed myositis, but the serum creatinine phosphokinase concentration was normal and histological examination of a biopsy specimen showed a subacute or chronic non-occlusive vasculitis (see figure). The muscle pains and fever abated within two days of starting steroids, and five days later the heart murmur had disappeared. Chest x-ray showed decrease in cardiac size, but her diabetic control had deteriorated. She developed sensory loss and weakness in the right leg and became confused and agitated. Steroids were reduced but fever returned and the