Comment

The cause of uraemic pruritus is unknown. In some cases it may be due to secondary hyperparathyroidism. Only in these patients is parathyroidectomy indicated.[2] The mechanisms of other treatments such as ultraviolet light[3] or cholestyramine[4] are unknown and are effective in only some cases. In our patient the rapid and complete disappearance of pruritus after lowering the dialysate magnesium concentration suggests a causative relation between itching and serum magnesium concentration. Lowering the dialysate magnesium concentration is known to restore nerve conduction velocity towards normal in patients receiving CHD,[5] and this could be the reason for the complete disappearance of the pruritus in our patient.

[1] Easton, P, and Galbraith, P R, *New England Journal of Medicine*, 1978, **299**, 1134.
[2] Massry, S G, *et al*, *New England Journal of Medicine*, 1968, **279**, 697.
[3] Gilchrest, B A, *et al*, *New England Journal of Medicine*, 1977, **297**, 136.
[4] Silverberg, D S, *et al*, *British Medical Journal*, 1977, **1**, 752.
[5] Stewart, W K, *et al*, *Proceedings of the European Dialysis and Transplant Association*, 1967, **4**, 285.

(*Accepted 19 September 1979*)

Second Medical University Clinic, Vienna, Austria
HELMUT GRAF, MD, resident in nephrology
JOSEF KOVARIK, MD, resident in endocrinology
HANS K STUMMVOLL, MD, registrar in nephrology
AXEL WOLF, MD, registrar in nephrology

A tube spacer to improve inhalation of drugs from pressurised aerosols

Inhalation from pressurised aerosols provides an effective means of drug administration with a low incidence of side effects, but many patients cannot co-ordinate inhalation with aerosol actuation.[1] Another potential disadvantage of pressurised aerosols is the deposition of drug on to the mucosa of the mouth and oropharynx caused by the high velocity of the flow of drug particles produced by aerosol actuation directly into the mouth. It has been shown,[2] however, that the interposition of a tube spacer between the aerosol and the mouth reduces deposition of drug and also that the drug remains suspended in the system for several seconds, thus enabling inhalation to be delayed after aerosol actuation. This study was designed to test the hypothesis that a tube spacer could improve drug inhalation in patients unable to use aerosols efficiently.

Patients, methods, and results

Sixteen patients with chronic asthma (age range 62-77 years, 10 men) were studied. All had a forced expiratory volume in one second (FEV_1) less than 70% of predicted normal, and the pretreatment FEV_1 did not vary by more than 12·5% between study days. Each patient received four separate treatments on different days. All bronchodilator treatment was withheld for 12 hours before each test. The order of treatment was randomised. The four treatments were: (*a*) 500 μg terbutaline from the conventional aerosol with actuation of aerosol at the beginning of inspiration; (*b*) 500 μg terbutaline from a conventional aerosol with a spacer 10 cm long and 3·2 cm in diameter attached—inhalation and actuation were co-ordinated; (*c*) 500 μg terbutaline from a conventional aerosol with a spacer 10 cm long and 3·2 cm in diameter attached—inhalation was delayed two seconds after actuation of aerosol; (*d*) 500 μg terbutaline from a conventional aerosol—inhalation was delayed two seconds after actuation of aerosol. FEV_1, forced vital capacity (FVC), peak expiratory flow rate (PEFR), and pulse rate were measured before and 5, 10, 20, 30, 60, 120, 180, 240, and 300 minutes after drug administration. Statistical analysis was carried out using a *t* test for paired comparisons.

The mean maximum increases in FEV_1, FVC, and PEFR are shown in the table. All treatments produced significant improvements at five minutes and the values remained above pretreatment levels for up to five hours. The rates of onset and duration of effects were similar for all treatments. The mean maximum increases in FEV_1, FVC, and PEFR were consistently higher after the co-ordinated use of the conventional aerosol and were significantly greater than the mean maximum improvements produced by the conventional aerosol uncoordinated. The mean maximum increases in the measurements of ventilatory function produced by the conventional aerosol used efficiently were not, however, significantly better than those after the use of the tube spacer co-ordinated or uncoordinated. The differences between the mean maximum increases in FEV_1, FVC, and PEFR after the use of the tube spacer co-ordinated and the conventional aerosol uncoordinated were not significant.

Influence of tube spacer and co-ordination on airways response to inhaled terbutaline sulphate. Results are means of maximum improvement (±SD), with statistical significance calculated as paired comparison to inhalation from aerosol co-ordinated

	Aerosol co-ordinated	Tube spacer co-ordinated	Tube spacer uncoordinated	Aerosol uncoordinated
FEV_1 (ml)	346±180	325±171 (NS)	319±173 (NS)	238±171 ($P<0·02$)
FVC (ml)	504±309	432±392 (NS)	459±193 (NS)	316±223 ($P<0·05$)
PEFR (l/min)	64±33	58±38 (NS)	46±37 (NS)	43±35 ($P<0·05$)

NS = Not Significant.

Comment

Many patients with bronchial asthma cannot use inhalers efficiently. At worst they expire at the time of actuation or at best actuation is not co-ordinated with the beginning of inspiration. In this study we used a compromise for inefficient administration of an inhaler in that inspiration was delayed by two seconds after aerosol actuation and this caused a significant reduction in efficacy when compared with the co-ordinated use of the aerosol. Nevertheless, there was no significant difference between the improvements in ventilatory function produced by the tube spacer without co-ordination and those produced by the conventional aerosol co-ordinated, though the mean values were consistently lower for the spacer.

These results show that the tube spacer can at least partially compensate for the artificially poor inhalation technique used in this study and suggest that this device may have a useful role in clinical practice. If further clinical studies confirm this the tube spacer will provide a much needed alternative to the dry powder inhaler.[3]

[1] Paterson, I C, and Crompton, G K, *British Medical Journal*, 1976, **1**, 76.
[2] Moren, F, *International Journal of Pharmaceutics*, 1978, **1**, 205.
[3] Hallworth, G W, *British Journal of Clinical Pharmacology*, 1971, **4**, 689.

(*Accepted 1 October 1979*)

Respiratory Diseases Unit, Northern General Hospital, Edinburgh
P BLOOMFIELD, MB, MRCP, research assistant
G K CROMPTON, MB, FRCPED, consultant physician

Astra Clinical Research Unit, Edinburgh
N J P WINSEY, BSC, PHD, clinical scientist

Clostridium difficile-associated colitis after neomycin treated with metronidazole

Clostridium difficile-associated colitis is being increasingly recognised after antibiotic treatment. The following case is the first to be documented after oral neomycin and was successfully treated with oral metronidazole.

Case report

A 65-year-old man with longstanding alcoholic cirrhosis was admitted with hepatic decompensation causing ascites and encephalopathy. Protein and salt restriction, oral lactulose, spironolactone, and neomycin (1 g four times daily) produced good improvement and he was discharged. Eight days after stopping neomycin he developed abdominal pain and bloody diarrhoea 8-10 times daily. This failed to settle over the next seven days, and on re-admission he was dehydrated, febrile, and jaundiced but had no encephalopathy. Sigmoidoscopy showed grossly active colitis with ulceration, pus, and bleeding to the limit of examination, but there was no pseudomembrane. A stool sample was cultured in Reinforced Clostridial Medium with 0·2% paracresol[1] and grew *Cl difficile* as identified morphologically and biochemic-

ally.[1] Enterotoxin, detected by its cytopathic effect on Hep2 cells in tissue culture and neutralisable by *Cl sordellii* antitoxin (Wellcome Foundation Research Laboratories), was found in the stool in high titre (table). Treatment was instituted with oral metronidazole 400 mg thrice daily and continued for 10 days. Within 36 hours the stool no longer contained visible blood and within three days was well formed. Sigmoidoscopy one week after beginning metronidazole showed a normal mucosa. After treatment the patient remained asymptomatic with no demonstrable *Cl difficile* organisms or toxin in the stool.

Stool cultures for Clostridium difficile and neutralisable Cl difficile toxin titres throughout metronidazole treatment

Duration of metronidazole treatment	Stool culture for *Cl difficile*	Neutralisable *Cl difficile* toxin titre in stool*
Pretreatment	Positive	1/1000
2 days	Positive	1/500
4 days	Negative	Nil
10 days	Negative	Nil
2 weeks after treatment	Negative	Nil

*One gram wet-weight stool extracted in 5 ml physiological saline.

Comment

Acute colitis, with or without pseudomembrane formation, associated with *Cl difficile* enterotoxin is an increasingly recognised complication of antibiotic treatment.[2] Lincomycin and clindamycin have been especially incriminated, but the role of other antibiotics including tetracycline, Co-trimoxazole, the cephalosporins, and the penicillins (particularly ampicillin) has also been well documented.[3] This case, in which oral neomycin is incriminated, re-emphasises the potential hazard of broad-spectrum antibiotics, especially when given specifically to alter the colonic bacterial flora and for hepatic failure. The dramatic response to oral metronidazole, with disappearance of organism and toxin together with symptomatic improvement, strengthens the case for using oral metronidazole in treating *Cl difficile*-associated colitis.[4]

I thank Dr R E Barry for permission to report this case and Dr P D Walker (Wellcome Foundation Research Laboratories) for providing *Cl sordellii* antitoxin.

[1] Hafiz, S, and Oakley, C L, *Journal of Medical Microbiology*, 1976, **9**, 129.
[2] *British Medical Journal*, 1979, **2**, 349.
[3] George, W L, *et al*, *American Journal of Clinical Nutrition*, 1979, **32**, 251.
[4] Pashby, N L, Bolton, R P, and Sherriff, R J, *British Medical Journal*, 1979, **1**, 1605.

(*Accepted 27 September 1979*)

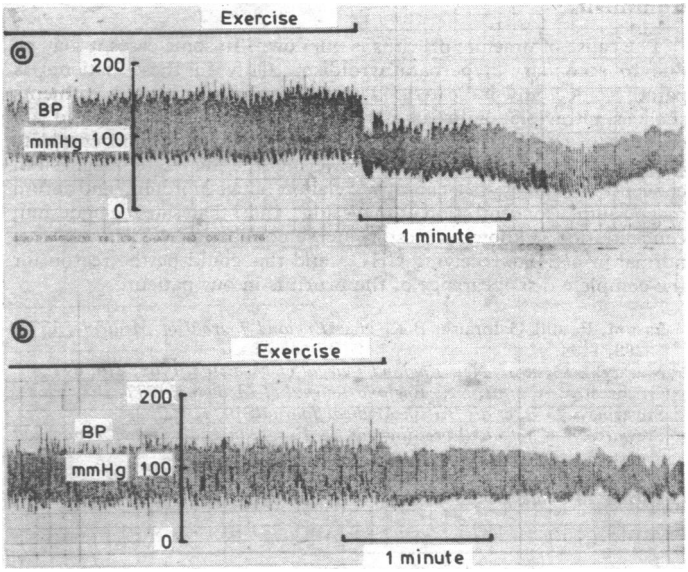
University Department of Medicine, Bristol Royal Infirmary, Bristol BS2 8HW
R P BOLTON, MA, MRCP, medical registrar

Syncope after running

Exertional hypotension is often seen in patients with various cardiac disorders[1] including severe coronary artery stenosis,[2] and in normal subjects during maximal exhaustive exercise. We describe a patient with mild ischaemic heart disease who developed syncopal episodes after running and a definite fall in blood pressure accompanying bradycardia after exercise.

Case report

A 48-year-old trained soldier was admitted on 7 May 1979 because of syncopal episodes after running. In the seven years before admission he had had several episodes of syncope while he was standing still after running 1-2 km, especially on cold mornings; he did not suffer syncopal attacks when he jogged instead of suddenly stopping running. Two years earlier he had been found to have an abnormal electrocardiogram, suggesting ischaemic heart disease, but he had no chest pain, palpitations, or shortness of breath even after running. He took no medication and continued his work and physical training. On examination he was well nourished and looked healthy. He was 163 cm tall and weighed 61 kg. His blood pressure was 100/58 mm Hg in the right arm and 100/56 mm Hg in the left. There was no orthostatic hypotension. Physical examination showed no abnormality except a grade 2 systolic murmur at the apex. Peripheral vessels were easily palpable and no bruit was heard. There was no neurological abnormality. Laboratory values were all normal, but he was positive for hepatitis B surface antigen.



(*a*) Fall of blood pressure with bradycardia after augmented 2-step test. (*b*) Disappearance of fall in blood pressure after pindolol.

At cardiac catheterisation the left ventriculogram and left ventricle end-diastolic pressure were normal. Coronary arteriography showed 50% stenosis of the left circumflex artery close to its origin and 25% stenosis in the right coronary artery. Direct brachial artery pressure measurement using a telemonitor showed a significant fall in blood pressure from 152/64 mm Hg during exercise (Master augmented 2-step test) to 100/40 mm Hg immediately after ceasing exercise. This lasted for 10-15 cardiac cycles and, after a transient increase, blood pressure then fell to 80/12 mm Hg with bradycardia for about one minute, when he felt light-headed but no syncope occurred (see figure, *a*). The fall of blood pressure after exercise disappeared by giving pindolol, 20 mg orally (figure, *b*).

His response to Valsalva manoeuvre, cold pressor test, and mental arithmetic test was normal. Plasma norepinephrine, epinephrine, and dopamine concentrations were, respectively, 260 ng/l, 25 ng/l, and 115 ng/l in a supine position and 706 ng/l, 98 ng/l, and 278 ng/l in an upright position for 10 minutes. Blood gas, plasma lactate, and plasma pyruvate values before and after exercise were normal.

Comment

Thomson and Kelemen[3] stated that a fall in systolic pressure during exercise is a sign that the left ventricular blood supply is severely compromised. Levites *et al*[2] found hypotension during exercise testing in 2·7% of the patients they tested, but the extent and distribution of coronary lesions were no different from those of patients with a normal blood pressure response to exercise. In their patients hypotension occurred during exercise but not after it. In our patient the extent of coronary artery narrowing was not significant and seemed unlikely to have caused the syncope and fall in blood pressure after exercise. His normal response to the Valsalva manoeuvre indicated an intact baroreceptor reflex arch. Another possible explanation of the syncope is a vasodepressor syncope associated with exercise. A beta-blocker prevented the fall in blood pressure and bradycardia in this patient, which suggested that the syncope may have been caused by a β-receptor-mediated neurogenic or metabolic mechanism induced by exercise.

[1] Bruce, R A, *et al*, *Circulation*, 1959, **19**, 543.
[2] Levites, R, Baker, T, and Anderson, G J, *American Heart Journal*, 1978, **95**, 747.
[3] Thomson, P D, and Kelemen, M H, *Circulation*, 1975, **52**, 28.

(*Accepted 2 October 1979*)

Department of Internal Medicine, Institute of Constitutional Medicine, University of Kumamoto, Kumamoto, Japan
ETSURO TSUTSUMI, MD, physician
HIROSHI HARA, MD, physician