

SHORT REPORTS

Comparison of actions of disodium cromoglycate and ketotifen on exercise-induced bronchoconstriction in childhood asthma

Ketotifen (Zaditen), a benzocycloheptathiophene derivative, is a new oral agent for treating asthma, with action similar in some respects to that of sodium cromoglycate. It is well established that sodium cromoglycate protects against antigen challenge by inhibiting the release of chemical mediators from mast cells. It also inhibits exercise-induced bronchoconstriction and has bronchodilator properties.¹ Ketotifen has a similar capacity to inhibit the release of chemical mediators from mast cells.² Its clinical effectiveness is still uncertain.^{3,4}

Patients, methods, and results

Twenty-three children with a clinical history of asthma and a value on the Jones lability index greater than 20% were examined. The decrease in peak expiratory flow rate (PEFR) below the resting value was examined and remeasured on another day after the child had been given 20 mg sodium cromoglycate solution via a Wright nebuliser and mains-driven compressor (Aerosol Products Ltd) 15 minutes before running. On a third day the test was repeated with 20 mg sodium cromoglycate powder given 15 minutes before exercise. It was repeated on a fourth day after the patient had received three days' treatment with ketotifen (1 mg twice a day by mouth). The last dose was given two hours before the test. The percentage fall index ((PEFR at rest - PEFR after exercise/PEFR at rest) × 100) was measured in each case.

Sodium cromoglycate solution was the most effective inhibitor and reduced the percentage fall index to a mean of 12% (see table). Sodium cromoglycate powder was less effective, and ketotifen was ineffective. The degree of inhibition varied considerably. In 14 of the children given sodium cromoglycate solution inhibition was virtually complete (a percentage fall of less than 10), whereas only three showed this level of inhibition in response to sodium cromoglycate powder and one to ketotifen.

Action of sodium cromoglycate and ketotifen in inhibiting exercise-induced bronchoconstriction in 23 asthmatic children

	Control	Sodium cromoglycate		Ketotifen
		Solution	Powder	
Mean fall (± 1 SD) in peak expiratory flow rate (l/min)	122 \pm 37	37 \pm 36	69 \pm 44	118 \pm 76
Mean % fall index (± 1 SD)	43 \pm 13	12 \pm 11	25 \pm 15	41 \pm 24

Control *v* cromoglycate solution: $p < 0.0005$; control *v* cromoglycate powder: $p < 0.0005$; control *v* ketotifen: $p > 0.1$; cromoglycate solution *v* ketotifen: $p < 0.0005$; cromoglycate solution *v* cromoglycate powder: $p = 0.001$; cromoglycate powder *v* ketotifen: $p = 0.003$.

Comment

The results showed a clear difference between ketotifen and sodium cromoglycate. Both are known to protect against antigen challenge, but only cromoglycate prevents exercise-induced bronchoconstriction. In the case of cromoglycate the solution was more effective than the powder, as previously shown.¹ Ketotifen may have proved ineffective against exercise-induced bronchoconstriction because it takes longer than three days to achieve its peak effect or because the dose was inadequate. These points may need further assessment, but higher doses would have to be considered in relation to the incidence of known side effects, in particular, drowsiness.

Sodium cromoglycate has been shown to have two distinct actions, one as an inhibitor of chemical mediator release from mast cells, and the other as a bronchodilator and inhibitor of exercise-induced bronchoconstriction, possibly due to more direct action on the bronchial muscle cells.¹ It is understandable that drugs that inhibit antigen challenge are likely to help the asthmatic. In this respect ketotifen and cromoglycate are effective, although relative potency will need further assessment. The capacity to inhibit exercise-induced bronchoconstriction is perhaps less obviously related to the clinical effectiveness of a drug. There is plenty of evidence, however, that the degree

of bronchial lability of an individual is a good indicator of pathophysiological state.⁵ Two drug actions are probably needed—protection against antigen challenge and action to induce bronchodilatation and inhibit exercise-induced bronchoconstriction. Ketotifen and sodium cromoglycate both possess the first, but only sodium cromoglycate possesses the second action.

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Overdose with ibuprofen causing unconsciousness and hypotension

Ibuprofen was introduced into Britain in 1967, and there have been no reported cases of overdosage. We report such a case, which resulted in depressed consciousness and hypotension.

Case report

A 70-year-old man presented one hour after ingesting about 30 400-mg tablets of ibuprofen. Blood was taken for ibuprofen estimation and gastric lavage performed. His consciousness then deteriorated rapidly and he responded only to painful stimuli. There were no localising neurological signs, reflexes were symmetrical, and plantar responses were flexor. Blood pressure fell from 120/80 to 80/60 mm Hg but central venous pressure remained constant at 6 cm H₂O. Examination of the abdomen and respiratory system showed nothing abnormal. He was treated with an infusion of dopamine 2 μ g/kg/min and his blood pressure rose to 110/70 mm Hg, but five hours later when the dopamine was discontinued it fell to 70/50 mm Hg. Dopamine was restarted at 2 μ g/kg/min and continued for a further 13 hours. By that time he had become fully conscious and blood pressure remained at 120/80 mm Hg when the dopamine was discontinued.

The initial serum concentration of ibuprofen was 840 mg/l (therapeutic range 20-30 mg/l), blood sugar 6.8 mmol/l (123 mg/100 ml), and calcium 2.5 mmol/l (9.8 mg/100 ml). A serum drug screen performed by the poisons unit, New Cross Hospital, on a sample taken three hours after admission identified only ibuprofen 220 mg/l, diazepam 0.47 mg/l, and nordiazepam (desmethyldiazepam) 0.07 mg/l (less than the normal therapeutic range). Faecal occult blood was not detected and serial electrocardiograms and cardiac enzyme activities were normal.

Comment

Many patients with rheumatological disorders are treated with ibuprofen. From this case apparently a depressed level of consciousness and hypotension may result soon after ingestion of more than the maximum dose. Side effects when taking the normal dose include headache, amblyopia, and lightheadedness but there is no record of depressed consciousness. The findings of Adams *et al*¹ in animals

suggest that ibuprofen has minor effects on the cardiovascular system, but our experience points to the contrary.

Care should be exercised in prescribing ibuprofen to people who are liable to take overdoses.

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¹ Adams SS, Bough RG, Cliffe EE, *et al.* Absorption and distribution and toxicity of ibuprofen. *Toxicol Appl Pharmacol* 1969;15:310-30.

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Plasma exchange to control sweats and pruritus in malignant disease

Pruritus and sweating attacks in malignant diseases such as the lymphomas are well recognised and disappear with successful treatment of the malignancy. Cimetidine, a potent histamine H₂-receptor antagonist, controls these symptoms in Hodgkin's disease,¹ but their pathogenesis is not explained. If pruritus and sweating were caused by metabolically active substances released into the plasma by the tumour such substances might be removed by plasma exchange.² We have tested this idea and report our preliminary findings.

Case reports

Case 1—A 54-year-old woman had non-Hodgkin's lymphoma (diffuse poorly differentiated lymphocytic) diagnosed in October 1977. She had left supraclavicular and epigastric masses and complained of general ill health and severe generalised itch. She initially responded well to cyclical administration of mustine hydrochloride, vinblastine, procarbazine, and prednisolone, with disappearance of the itch; but this and subsequent responses to chlorambucil, vinblastine, procarbazine, and prednisolone and then doxorubicin, bleomycin, vincristine, and dacarbazine were not maintained. In autumn 1979 she received palliative radiotherapy to an abdominal mass. General ill health, wasting, and intractable itch continued, the itch being unrelieved by cimetidine 800 mg daily. A therapeutic trial of plasma exchange was conducted with a Hemonetics model 30 cell processor, with human pooled fresh-frozen plasma as replacement solution. On the first occasion 4.9 l plasma was removed, and eight days later 4.3 l. Itching disappeared after the first exchange and remained virtually absent for several weeks. No other treatment was given. She died two months after the plasma exchange.

Case 2—A 53-year-old man had a left nephrectomy for renal carcinoma in April 1979. Radiography showed numerous small discrete lung metastases and he was treated for four months with iphosphamide at three-week intervals, with no evidence of progression. Lung metastases then enlarged and tamoxifen was substituted but discontinued after only two months because of progressive disease. There was a painless mass in the nephrectomy scar 5 × 4.5 cm. His only notable symptom was severe night sweats. Plasma exchange performed as in case 1 (3.4 l plasma removed initially) resulted in an immediate and sustained reduction in the number and severity of night sweats, with only light sweating occurring not more than twice weekly. Four further plasma exchanges (3.3, 4.6, 4.0, and 3.6 l) were conducted over the next nine weeks. The mass in the nephrectomy scar regressed to 4 × 3 cm, but the lung metastases continued to enlarge. No other treatment was given. Medroxyprogesterone acetate 100 mg thrice daily was prescribed two weeks after the fifth plasma exchange, though the light sweating at night had not increased beyond twice a week.

Comment

From these observations plasma exchange may control severe itching or sweating in advanced malignancy when drugs have failed to do so. This apparently confirms the suggestion that itching and sweating are caused by circulating factors produced by the tumour or as a host response, though it does not exclude the possible effect of an active blocking factor added by the fresh-frozen plasma. The results justify further investigation of plasma exchange to elucidate the

mechanisms producing the symptoms. It may be possible to isolate circulating factors in extracorporeal blood with in-series selective affinity columns³ and use dialysis of exchanged plasma to establish their nature and physical characteristics.

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¹ Aymard JP, Lederlin P, Witz F. Cimetidine for pruritus in Hodgkin's disease. *Br Med J* 1980;280:151-2.

² Trotter JM, Shaw D, Carlyle E, Shephard J, Calman KC. Nutritional aspects of plasma exchange in cancer patients. In: Serrou B, ed. *Immune complexes and plasma exchange in cancer patients*. Amsterdam: Elsevier/North Holland (in press).

³ Terman DS, Yamamoto T, Mattioli M. Extensive necrosis of spontaneous canine mammary adenocarcinoma after extracorporeal perfusion over *Staphylococcus aureus* cowans I. *J Immunol* 1980, 124:795-805.

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Oxprenolol and retroperitoneal fibrosis

Retroperitoneal fibrosis is a fairly rare cause of impaired renal function. Methysergide taken for migraine¹ and also abuse of analgesic drugs have been implicated in some earlier cases. Recently it has been reported in patients who had taken the beta-blocker atenolol.^{2,3} We report retroperitoneal fibrosis occurring in a patient who had been taking oxprenolol for five years.

Case report

In June 1979 a 53-year-old male charge nurse was referred by his general practitioner because of a persistently raised blood urea concentration of 23.0 mmol/l (140 mg/100 ml), mild anaemia (haemoglobin 10.1 g/dl), and raised erythrocyte sedimentation rate (ESR) at 62 mm in 1 h, Westergren. He had suffered from angina pectoris for four years and mild ankle swelling in the preceding 6 months. In 1974 he had been started on oxprenolol 80 mg twice daily for hypertension. In 1978 oxprenolol had been changed to Slow Trasicor 160 mg once daily, and for about the past six months he had also been taking Adalat 10 mg three times daily and Hygroton K 50 mg once daily.

When referred to us his blood urea was 20.0 mmol/l (120 mg/100 ml), haemoglobin 10.7 g/dl, serum creatinine 340 μmol/l (3.4 mg/100 ml), and his creatinine clearance was 31 ml/min. He was admitted for investigation. Clinical examination was unremarkable. His blood pressure was well controlled at 120/70 mm Hg and his pulse regular at 72/min. His ESR was 114 mm in 1 h. A high-dose intravenous pyelogram showed poor excretion of contrast medium by both kidneys, a large left-sided hydronephrosis, and the ureters displaced medially. Retroperitoneal fibrosis was diagnosed and confirmed at operation, when dense fibrous tissue was found extending retroperitoneally down into the pelvis and around both ureters. Multiple specimens of tissue were taken for biopsy and bilateral ureterolysis performed. Biopsy specimens showed dense collagenous, relatively acellular fibrous tissue with no evidence of vasculitis and no malignant cells. The appearances were typical of retroperitoneal fibrosis. Postoperative recovery was uneventful and he was discharged well without a hypotensive drug. At follow-up two months later his blood urea concentration had fallen to 11.0 mmol/l (66 mg/100 ml) and serum creatinine concentration to 215 μmol/l (2.15 mg/100 ml), and his creatinine clearance had increased to 42 ml/min. Clinically the only abnormal finding was a blood pressure of 170/100 mm Hg. He was started on a thiazide diuretic. The only other drug he has taken since is glyceryl trinitrate for angina pectoris.

Comment

The histological appearance of retroperitoneal fibrosis occurring in association with ingestion of methysergide does not differ from that not known to be associated with drug ingestion. The appearance of