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 ± 37	37 ± 36	69 ± 44	118 ± 76
Mean % fall index (±1 SD)	43 ± 13	12 ± 11	25 ± 15	41 ± 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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¹ Chung JTN, Jones RS. Bronchodilator effect of sodium cromoglycate and its clinical implications. *Br Med J* 1979;ii:1033-4.

² Martin U, Roemer E. Ketotifen: a histamine release inhibitor. *Monogr Allergy* 1977;12:145.

³ Craps L, Greenwood C, Radielovic P. Clinical investigation of agents with prophylactic antiallergic effects in bronchial asthma. *Clin Allergy* 1978; 8:373.

⁴ Dyson AJ, Mackay AD. Ketotifen in adult asthma. *Br Med J* 1980;280: 360.

⁵ Jones RS. Assessment of respiratory function in the asthmatic child. *Br Med J* 1966;iii:972.

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Respiratory Unit, Alder Hey Children's Hospital and University Department of Child Health, Liverpool L12 2AP

J D KENNEDY, MB, DCH, research assistant (present address: Leicester Royal Infirmary)

F HASHAM, MRCP, DCH, research assistant

M J D CLAY, technician in respiratory physiology

R S JONES, MD, FRCP, consultant paediatrician and director of studies in paediatric science

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 µg/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 µg/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