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# A comparison of ketotifen with clemastine, ipratropium bromide and sodium cromoglycate in exercise-induced asthma

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**Summary**

Exercise-induced asthma (EIA) was provoked by a standardized treadmill running for 8 min in seven atopic adult asthmatics. The tests were performed using a double-dummy technique after placebo, oral ketotifen, inhaled clemastine, ipratropium bromide and sodium cromoglycate (SCG), in a random single blind-fashion on different days. The mean post-exercise percentage fall in forced expiratory volume in 1 sec ($FEV_1$) was 47 (s.e. 6·95), 39 (s.e. 8·35), 27 (s.e. 7·17), 23 (s.e. 7·69) and 7·0 (s.e. 4·62)% respectively. There was significantly less mean bronchoconstriction with SCG ($P < 0·01$), ipratropium bromide and clemastine ($P < 0·05$) but not with ketotifen. Six out of seven individual patients had significant protection of EIA with sodium cromoglycate, four with ipratropium bromide, three with clemastine but only one with ketotifen. Ipratropium bromide and clemastine were bronchodilators at rest, whereas SCG and ketotifen were not. Despite its claims to work as a mast cell stabilizing drug, ketotifen in a single dose does not have an effect similar to sodium cromoglycate in EIA, nor does it compare with inhaled clemastine or ipratropium bromide.

## Introduction

Ketotifen is a recently introduced drug for treatment of asthma. It has been shown to be a mast cell stabilizer *in vitro* with strong antihistamine effects (Martin & Römer, 1978). Though it protects against antigen and histamine challenge in asthmatics (Craps, Greenwood & Radielovic, 1978), its therapeutic efficacy in clinical practice is still open to question (Dyson & MacKay, 1980). We report on a comparison between ketotifen and an anticholinergic agent, ipratropium bromide (IB), an antihistamine, clemastine and a mast cell stabilizing drug, sodium cromoglycate (SCG) in exercise-induced asthma (EIA).

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**Patients and methods**

Seven patients aged between 11–35 years with skin test-positive allergic asthma and known to have an exercise-induced fall in forced expiratory volume in 1 sec ($FEV_1$) of more than 25% were studied. All were non-smokers and gave informed consent. Patients on oral or inhaled corticosteroids were excluded. Sodium cromoglycate and bronchodilator drugs were discontinued for 24 hr before each test. Levels of $FEV_1$ were measured with a water-sealed spirometer (Godart Pulmotest). The best of three attempts were used for analysis and volumes were corrected to body temperature and pressure saturated.

Exercise-testing consisting of steady-state running on an inclined treadmill (10°) for up to 8 min. Speed was adjusted so that pulse rate at the end of exercise was at least 170–180/min (submaximal work load). The same setting and duration was used for each test in any one patient. Room temperature on study days varied between 20–22°C with 30–50% relative humidity. The study was carried out in a random single blind-fashion.

Patients were given ketotifen or placebo tablets, 90 min prior to exercise followed by inhalation of SCG, IB, clemastine or saline as placebo, 30 min later, 1 hr prior to exercise. Details of drug administration are given in Table 1. The inhaled drugs were

**Table 1.** Administration and dose of the drugs

| Drug | Route of administration | Concentration | Estimated total dose |
|---|---|---|---|
| Saline | Nebulized | 9·0 g/l | — |
| SCG | Nebulized | 10 g/l | 12 mg |
| IB | Nebulized | 0·1 g/l | 120 μg |
| Clemastine | Nebulized | 1·0 g/l | 1·2 mg |
| Ketotifen | Oral | — | 2·0 mg |

delivered through a Wright's nebulizer driven by compressed air at 9·0 l/min (18 psi). All inhalations were carried out for 5 min at tidal breathing. Spirometry was performed before the oral tablets, prior to inhalation and exercise, and at 2, 5, 10, 15 and 30 min after exercise. Results of the exercise tests were expressed as the maximum fall in $FEV_1$ from the post-drug resting baseline and analysed with Student's paired *t*-test. The degree of protection of each drug was calculated from the following formula:

$$\text{Protection (\%)} = \frac{\text{Fall on placebo (\%)} - \text{Fall on drug (\%)}}{\text{Fall on placebo (\%)}} \times 100$$

**Results**

The mean results are given in Table 2. After administration of IB and clemastine there was a significant degree of bronchodilatation with mean rises of 11% ($P < 0{\cdot}01$) and 4·5% ($P < 0{\cdot}02$) respectively. There was no alteration of $FEV_1$ with saline, sodium cromoglycate or ketotifen. The effect of the drugs on mean resting $FEV_1$ is shown in Fig. 1, which also shows the percentage fall in $FEV_1$ after exercise from the pre-drug baseline. After exercise there was a mean 47% drop in $FEV_1$ with saline but this

**Table 2.** Effect of saline, sodium cromoglycate, ipratropium bromide, clemastine and ketotifen on $FEV_1$ before and after exercise

| | Saline | | | | SCG | | | | IB | | | | Clemastine | | | | Ketotifen | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $FEV_1$ (l) | A* | B† | C‡ | Fall§ | A | B | C | Fall | A | B | C | Fall | A | B | C | Fall | A | B | C | Fall |
| Mean | 2·98 | 2·94 | 2·88 | 1·36 | 2·83 | 2·83 | 2·84 | 0·21 | 2·81 | 2·81 | 3·13 | 0·74 | 2·85 | 2·85 | 2·98 | 0·83 | 2·88 | 2·85 | 2·91 | 1·12 |
| Standard error of mean | 0·38 | 0·37 | 0·36 | 0·29 | 0·51 | 0·47 | 0·46 | 2·09 | 0·33 | 0·34 | 0·37 | 0·24 | 0·44 | 0·43 | 0·43 | 0·33 | 0·42 | 0·40 | 0·48 | 0·30 |

* A = baseline before treatment
† B = baseline 30 min after oral tablet
‡ C = baseline 90 min post-oral tablet 60 min after inhalations
§ Fall from C

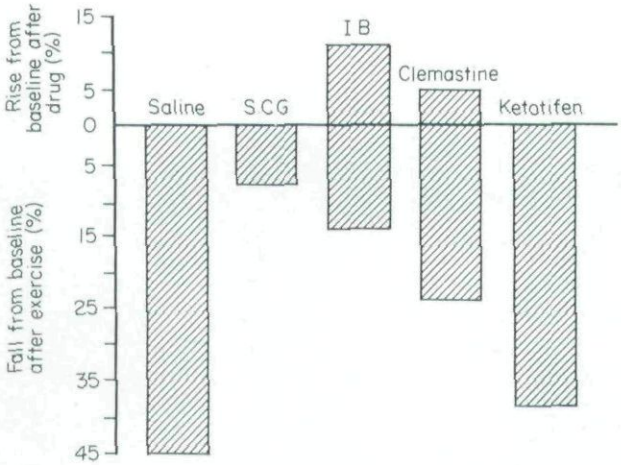


**Fig. 1.** Percentage mean change of $FEV_1$ from baseline (○) before any drug.

reduction was significantly less with SCG ($P<0{\cdot}01$), IB ($P<0{\cdot}05$) and clemastine ($P<0{\cdot}05$) (Table 3). Ketotifen did not significantly inhibit exercise-induced bronchospasm.

Calculation of the degree of protection shows an 85% mean protection with SCG, 51% with IB, 42% with clemastine. Individual responses to each drug are given in Table 4.

Patient No. 1 had no protection with any of the drugs, whereas six patients blocked well with SCG, four with IB, three with clemastine. Only one patient out of seven had more than 50% protection with ketotifen.

**Table 3.** Percentage maximum fall in $FEV_1$ after exercise (% protection given in parentheses)

| Patient No. | Age | Sex | Saline | SCG | IB | Clemastine | Ketotifen |
|---|---|---|---|---|---|---|---|
| 1 | 32 | F | 44 | 35 (20) | 43 (0) | 34 (23) | 37 (16) |
| 2 | 15 | F | 64 | 6·0 (90) | 55 (14) | 44 (31) | 65 (0) |
| 3 | 33 | F | 25 | 10 (60) | 4·0 (84) | 23 (8) | 27 (0) |
| 4 | 22 | F | 56 | 1·0 (98) | 2·0 (96) | 4·0 (92) | 55 (0) |
| 5 | 20 | M | 55 | 3·0 (98) | 25 (54) | 51 (7) | 36 (34) |
| 6 | 11 | M | 64 | 4·0 (93) | 12 (81) | 31 (51) | 57 (10) |
| 7 | 35 | F | 18 | 3·0 (83) | 24 (0) | 1·0 (94) | 1·0 (94) |
| Mean | | | 47 | 7·0 (85) | 23 (51) | 27 (42) | 39 (17) |
| Standard error of mean | | | 6·95 | 4·62 | 7·69 | 7·17 | 8·35 |

## Discussion

Sodium cromoglycate (SCG), IB and clemastine significantly inhibited mean bronchoconstriction in seven patients with EIA. Ketotifen had no mean inhibitory effect. One patient was not protected from EIA by any of the drugs, whereas six patients inhibited

**Table 4.** Individual significance of response compared with saline

| Patient No. | DSG | IB | Clemastine | Ketotifen |
|---|---|---|---|---|
| 1 | 0* | 0 | 0 | 0 |
| 2 | ++‡ | 0 | +† | 0 |
| 3 | ++ | ++ | 0 | 0 |
| 4 | ++ | ++ | ++ | 0 |
| 5 | ++ | ++ | 0 | + |
| 6 | ++ | ++ | ++ | 0 |
| 7 | ++ | 0 | ++ | ++ |
| Mean | ++ | ++ | + | 0 |

* 0 = < 25% protection
† + = 25–50% protection
‡ + + = > 50% protection

well with SCG, four with IB and three with clemastine. Only one patient had any significant protection from ketotifen.

The mechanism of EIA is unknown. The initial stimulus is thought to be hyperventilation (Zeballos *et al.*, 1978) with subsequent cooling of the airways (McFadden & Ingram, 1979). Both a vagal reflex stimulation of irritant receptors or direct mediator-release from the lung mast cells have been postulated as the next step towards bronchospasm. The vagal influence seems only to be important in two-thirds of patients (Hartley & Davies, 1980) as the anticholinergic drugs atropine and IB only inhibit between 50–75% of patients with EIA (Godfrey & König 1976). The vagal mechanism is most significant in those patients whose main site of airflow obstruction is the large airways (McFadden *et al.*, 1977; Thomson, Patel & Kerr, 1978). Four out of our seven patients inhibited with IB while patient no. 7 in our study inhibited with ketotifen and clemastine, but not at all with IB, suggesting that a different mechanism may be important in this patient's EIA.

Mast cell degranulation, whether secondary to vagal stimulation or to the direct effect of cooling on the mast cell and subsequent release of mediators such as histamine, is thought to be the final common pathway for bronchoconstriction. Direct evidence for mediator release has not yet been clearly shown. Histamine levels measured during EIA have shown conflicting results (Clarks *et al.*, 1979; Ferris, Anderson & Temple, 1978; Harries *et al.*, 1979). Histamine may be released into the circulation in too small an amount and metabolized too rapidly for it to be easily assayed. However, the excellent protective effect of SCG in EIA suggests that mediator release is important. Further supportive evidence, suggesting depletion of mediator stores in the mast cell after EIA, is provided by the reduced bronchoconstriction that occurs when exercise is repeated at a short interval (McNeil *et al.*, 1966) and the existance of a refactory period after EIA when it is much less easy to induce an attack (Edmunds *et al.*, 1978).

Oral antihistamines appear to have no inhibitory effect on exercise induced asthma (McNeil *et al.*, 1966; Craps *et al.*, 1978). However, clemastine given by inhalation protects against EIA in a percentage of patients (Hartley & Nogrady, 1980) as in our

study where three out of seven patients were well protected. Though clemastine is a bronchodilator it seems likely that it works by its antihistamine effect as it blocks histamine-induced bronchoconstriction but not methacholine-induced bronchoconstriction (Nogrady & Bevan, 1978). Ketotifen in our patients failed to inhibit EIA in a similar manner to clemastine.

Ketotifen is a mast cell stabilizing drug *in vitro* (Martin & Römer, 1977). Sodium cromoglycate blocks EIA in about 80% of patients and is thought to work like ketotifen by its mast cell stabilizing properties (Davies, 1968). Craps *et al.* (1978) compared 3 days of oral ketotifen with inhaled SCG in adults and found that ketotifen gave good protection against EIA in more than 70% of patients, giving similar results to SCG. However, Kennedy *et al.* (1980) using the same dose of 1·0 mg twice daily for 3 days found ketotifen to be completely ineffective in children with EIA. In our study, six out of seven patients inhibited with one dose of SCG, but only one with ketotifen suggesting little similarity between the acute effect of ketotifen and SCG. However, ketotifen has a slow onset of action. It has been proposed that up to 6 weeks are needed before optimal efficacy has been reached (Cameron, 1981). Ketotifen may have a long term non-specific effect modifying bronchial reactivity in the same way that SCG alters bronchial reactivity with prolonged use (Altounyan, 1979).

Thus, ketotifen in a single oral dose of 2·0 mg does not inhibit EIA, while inhaled SCG, IB and clemastine do to a varying degree. Ketotifen does not act acutely as a mast cell stabilizing drug like SCG in EIA. However, as it may alter bronchial reactivity with time, further long-term studies are required to assess its role in inhibiting exercise induced asthma.

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