

Double-blind comparison of the protective effect of sodium cromoglycate and ketotifen on exercise-induced asthma in adults

W. C. TAN and T. K. LIM

Respiratory Medicine Unit, Department of Medicine, National University of Singapore, Singapore

In a double-blind double-placebo study 10 asthmatics exercised on a treadmill after treatment for 1 week with placebo, or ketotifen 1 mg twice daily, or SCG 10 mg four times daily. The post-exercise percentage fall in FEV₁ after SCG but not after ketotifen was significantly smaller than after placebo. A 1-week treatment with SCG but not ketotifen protected against EIA.

Key words: exercise-induced asthma; ketotifen; sodium cromoglycate.

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The protective effect of sodium cromoglycate (SCG) on exercise-induced asthma (EIA) is well documented in asthmatic children and adults (2, 3, 14) but the role of ketotifen in EIA is less well defined. Several single-blind studies showed that ketotifen gave little protection against EIA (5, 6, 11) while one double-blind study found that ketotifen was as effective as SCG in preventing exercise-induced asthma in children (13). We compared the effects of these two drugs on EIA in asthmatic adults.

PATIENTS AND METHODS

Ten adults (7 men, 3 women), age range 16-44 years (mean age 23 years), entered the study. All had clinically recognisable asthma and were receiving regular inhaled β_2 -agonist. All had exercise-induced asthma with a post-exercise fall in FEV₁ > 20% of the highest FEV₁ measured immediately after exercise (4). Only those patients with a resting FEV₁ not less than 70% of the predicted value were studied. All patients gave informed consent to the study, which was approved by the clinical trial committee of Singapore.

The study was a double-placebo, double-blind cross-over with patients randomised to treatment order according to a latin square design. All medications were discontinued 8 h before the exercise. The patients exercised at about the same time of day on four occasions at intervals of 7 days: a control run and after treatment for 1 week with each of three treatments. These consisted of active SCG aerosol 10 mg (2 puffs) four times daily (qds) plus placebo syrup 5 ml twice daily (bd); ketotifen syrup 1 mg (5 ml) bd plus placebo aerosol qds; and placebo syrup plus placebo aerosol. The last dose of each treatment was administered in the laboratory: syrup 3 h before and aerosol half an hour before the test.

Standardized treadmill exercise (8) was performed for 6 min at 23-25°C and relative humidity 60-63%. FEV₁ was measured with a dry spirometer (Minato, Japan) before exercise, immediately after and at 2, 5, 10, 15 and 30 min after exercise.

The treatment effects were assessed from changes in lung function after exercise. The changes were calculated by expressing the maximum fall in FEV₁ after exercise as a percentage of the highest FEV₁ measured immediately after

exercise (TB index) (4). Student's t test for paired data was used for comparison of the maximum % fall in FEV₁ (Table 1).

RESULTS

There was no difference in the mean heart rates during four exercise tests: control 165 (SEM 2) per min, placebo 166 (3), SCG 162 (3), ketotifen 163 (3). The mean post-treatment pre-exercise FEV₁ on each occasion did not differ significantly: control 2.56 (0.18) l, placebo 2.38 (0.16) l, SCG 2.44 (0.15) l, ketotifen 2.50 (0.16) l. Mean FEV₁ before and for 30 min after exercise is shown in Fig. 1. The lowest FEV₁ was recorded at 5 min after exercise for SCG but at 10 min for placebo and ketotifen. The individual maximum % falls in FEV₁ were expressed as TB indices and shown in Table 1. The mean % fall in FEV₁ after exercise for SCG was significantly less than the placebo value *P* < 0.003), but there was no difference between the values for ketotifen and for placebo.

DISCUSSION

Both ketotifen and sodium cromoglycate (SCG) are used as prophylactic treatment for asthma. While the protective effect of SCG on EIA is well established (2, 3, 14) the effect of ketotifen appears to be less consistent (5, 11, 13, 15).

Table 1

Maximum percentage falls in FEV₁ (TB index) after treadmill exercise in 10 asthmatic adults without treatment and after pretreatment with placebo, sodium cromoglycate, or ketotifen

Patient	No drug	Placebo	SCG	Ketotifen
1	33	41	25	49
2	56	59	50	66
3	39	40	26	57
4	47	44	27	38
5	43	53	16	60
6	37	23	18	24
7	36	31	20	20
8	27	23	25	65
9	50	49	26	46
10	33	19	8	29
Mean	40	38	24	45
SEM	2.8	4.3	3.4	5.4

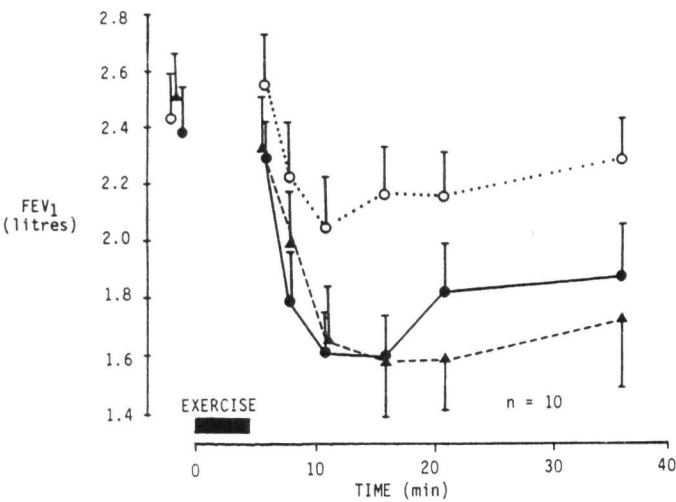


Fig. 1. FEV₁ before and after treadmill exercise in 10 asthmatic patients after pretreatment with placebo ●—●, ketotifen ▲—▲, sodium cromoglycate ○—○.

In the present study sodium cromoglycate produced smaller reductions in FEV₁ after exercise when compared with that of placebo. This supports the consensus opinion that SCG protected against EIA. We also found some inter-patient variability in the magnitude of protection shown by SCG. This heterogeneity in the response to exercise of asthmatic patients after pre-treatment with SCG has also been observed by other workers (2). Although our patients received SCG aerosol four times daily for 1 week, the last aerosol dose was given 30 min before exercise. It is therefore conceivable that the protective effect of SCG was an acute effect.

Our finding that ketotifen was no better than placebo agreed with that of Dorward & Patel (6) but not that of Lilja et al. (13).

There may be two possible explanations for the failure of ketotifen to prevent EIA. Ketotifen was administered orally, and although exercise was performed at a time aimed to coincide with an anticipated peak plasma concentration (10), this may not necessarily reflect the concentration of the drug in the airways as has been observed in studies which showed differences in the protective efficacy of oral and inhaled salbutamol on EIA (1). Another explanation is that the action of ketotifen in EIA differs from SCG. Since our study commenced, Dorward & Patel (7) have shown that ketotifen at a dose of 1 mg twice daily for 9 weeks protected against EIA. This effect resembles

that of inhaled corticosteroids, which had no effect when given as a single dose before exercise (12) but which protected against EIA after a month's prolonged treatment (9).

Further double-blind studies comparing the effect of ketotifen on EIA with that of placebo after treatment for several months may clarify the role of this drug in EIA.

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Address:

Dr. W. C. Tan

Respiratory Medicine Unit

Department of Medicine

National University Hospital

Lower Kent Ridge

Singapore 0511

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