

Comparison of the Protective Effect of Ketotifen and Disodium Cromoglycate on Exercise-Induced Asthma in Asthmatic Boys

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Fourteen boys with a mean age of 12.2 years were studied with respect to the protective effect of ketotifen on exercise-induced asthma (EIA) in comparison with disodium cromoglycate (DSCG). All had a positive history of EIA and a post-exercise fall in FEV₁ of more than 20%. A double blind cross-over technique was used with a 1 week wash-out period between the two treatment alternatives. Both drugs gave some, but not significant protection for EIA and no differences between the two active substances tested were found. Great individual differences in the response to the two drugs were noted.

Key words: asthma; childhood; disodium cromoglycate; exercise-induced asthma; ketotifen.

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In asthmatic individuals exercise-induced asthma (EIA) can be provoked by physical exercise (2, 12). Especially in children with bronchial asthma this can act as a limiting factor for their physical activity. It is therefore of great importance that the anti-asthmatic medical treatment gives protection not only for allergen-induced bronchospasm but also for EIA. Ketotifen has been shown to have good protective properties on childhood asthma during the deciduous tree pollen season (7) and in adults it has been reported to offer acceptable protection against EIA (5, 13).

The aim of the present investigation was to determine whether ketotifen offers acceptable protection against EIA in asthmatic children using disodium cromoglycate (DSCG) as a reference substance.

PATIENTS

Fourteen boys with perennial bronchial asthma, aged 12.2 ± 1.1 years (range 10.0-13.5), all outpatients at the Sachs' Childrens Hospital

Table 1
Baseline expiratory flow values for 14 boys with bronchial asthma at the time for selection of the material (visit 1) in comparison with predicted values (3). (Mean values ± 1 SD)

		Mean	+ SD	Percent of predicted value
FEV ₁	Predicted	2.84	0.54	77
	Observed	2.19	0.38	
FVC	Predicted	3.35	0.66	83
	Observed	2.78	0.36	
FEV %	Predicted	85.1	1.1	92
	Observed	78.4	8.2	

and the Pediatric Clinic Huddinge Hospital, were studied. The mean duration of asthma symptoms was 8.0 ± 2.4 years. Criteria for inclusion in the investigation were a positive history of EIA and a post-exercise decrease in

the forced expiratory volume during the first second (FEV₁) of more than 20%. The mean maximal decrease of FEV₁ after exercise during basal conditions was 42%, indicating that the boys studied had pronounced EIA. The mean values of the baseline lung function parameters are given in Table 1. In 12 out of the 14 boys one or more exogenous allergens for triggering allergic reactions were identified by positive skin prick test and/or bronchial provocation. One of the two boys with negative prick test had positive RAST (Phadebas) for several allergens. The study was approved by the Committee of Ethics at the Karolinska Institute.

METHODS

Two treatment alternatives were given, one consisting of ketotifen as the active substance in tablet form in a dose of 1 mg twice a day and placebo for DSCG (lactose) given as inhalation four times a day. The other alternative consisted of DSCG as active substance given by inhalation in a dose of 20 mg four times a day and placebo (lactose) for ketotifen given as a tablet twice a day.

Scoring cards were used for the daily registration of asthmatic symptoms and additional anti-asthmatic medication taken during the whole observation period.

Exercise was performed on an electrically braked bicycle ergometer (Elema) at a pedalling rate of 60 r/m.

Heart rate at rest and during exercise were measured on ECG tracings. Dynamic lung function in terms of forced vital capacity (FVC) and FEV₁ were determined using a Vitalograph dry spirometer as the recording unit. The best value of two consecutive measurements was registered. The FEV₁, expressed as percentage of the VC, FEV%, was calculated. Determinations were made before the exercise tests, thus establishing the basal expiratory flow level and after exercise, every 5 min for half an hour. No determinations were made during exercise. Statistical calculations were made using the Student's t-test for paired observations.

PROCEDURE

The design followed was double blind and cross-over (Fig. 1). The patients selected for the investigation were randomly allocated into two groups, one starting with ketotifen as the active substance and the other with DSCG. The treatment periods before the exercise tests were 1 week long with a wash-out period of 1 week between the two treatment alternatives. The last tablet of ketotifen or placebo, was given 2–3 h before the exercise testing and the last capsule of active DSCG or placebo powder was inhaled 20 min before the test started. In seven boys, who were on treatment with DSCG, this substance was withdrawn 3 weeks before the study started. No beta₂-agonists or theophyllines were

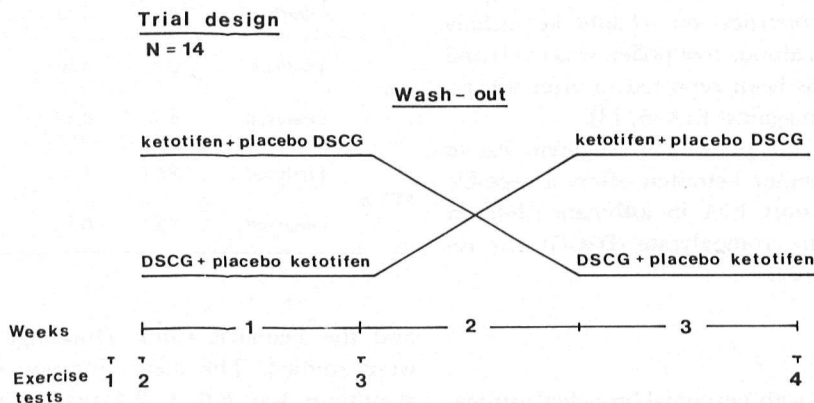


Fig. 1. Trial design for double blind cross-over study of the protective effect of ketotifen and DSCG on EIA in 14 boys with bronchial asthma.

given at least 12 h before the laboratory investigations.

Exercise tests were performed on four occasions under standardized conditions (Fig. 1). At the first test the maximal working capacity was identified by raising the work load in steps of 10 w/min until no further increase in heart rate was seen, heart rate ≥ 190 beats/min. At the following three visits the boys performed 6 min exercise tests at 80% of the maximal working level. A 1-min "warming up" period at 20–30 w preceded the submaximal work test. Only patients responding with a post-exercise fall in FEV₁ at the second visit (control test) exceeding 20% were finally selected. No pre-treatment with placebo was performed at this test. All exercise tests were made at the same time of the day in each patient. Air temperature and humidity were not standardized at the different exercise tests. No part of the study was performed during the pollen season.

RESULTS

The mean decrease in FEV₁ 5 min after exercise was 40% under control conditions (visit 2), 31% after pre-treatment with ketotifen and 28% after pre-treatment with DSCG (Fig. 2). The differences in the post-exercise decrease in FEV₁ between the control test and the corresponding tests after 1 week of treatment with ketotifen and DSCG respectively, or between the two treatments, were not significant. During control conditions the mean fall in FVC 5 min after exercise was 29%, after 1 week on pre-treatment with ketotifen 21% and after 1 week on DSCG 19% (Fig. 3). The mean decrease in FEV% under control conditions was 17%, after ketotifen 13% and after DSCG 12%. As for FEV₁ the differences were not significant.

The basal FEV₁-levels were found to be higher after pre-treatment with ketotifen (2.20 ± 0.45 l) and DSCG (2.14 ± 0.36 l) than without any premedication (2.02 ± 0.37 l), the difference between the basal ketotifen and control levels being statistically significant ($P < 0.05$). The higher basal FEV₁-levels of the 1 week of ketotifen or DSCG may be regarded as

Changes in FEV₁
% of basal value

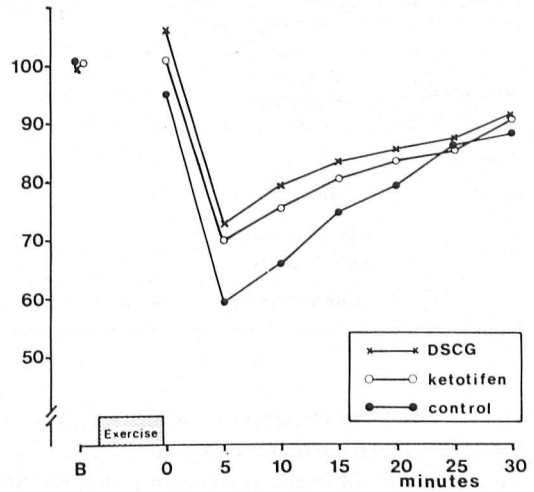


Fig. 2. Changes in FEV₁ after 6 min submaximal exercise as per cent of pre-exercise basal values. No differences between the three conditions are significant.

Changes in FVC
% of basal value

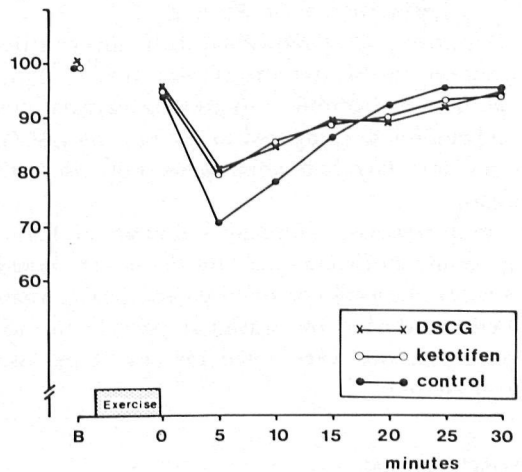


Fig. 3. Changes in FVC after 6 min submaximal exercise as per cent of pre-exercise basal values. No differences between the three conditions are significant.

a therapeutic effect of the drugs given and/or as a placebo effect.

In order to study not only the maximal decrease of the expiratory flow during the dif-

Table 2

Different degrees of protection against EIA after pretreatment with ketotifen and DSCG in 14 boys with bronchial asthma

Protection	Post-exercise decrease in FEV ₁	Ketotifen	DSCG
Complete	< 10%	2	2
Good	10–20%	1	4
Some	> 20% but less than control exercise	4	2
No	≥ Control exercise	7	6

ferent conditions but also the development over time, the mean changes from the pre-exercise values for the different observations over the 30 min post-exercise period (area under the curve) for FEV₁, FVC and FEV% were also calculated. No differences between the various conditions were found (paired t-test).

Two boys in each group had complete protection for EIA and five in the ketotifen and six in the DSCG groups had good to some protection. Seven respectively six boys in each group had no protection at all (Table 2).

However, great individual differences in the response to the two drugs were noted. Thus, two boys had complete to good protection only on ketotifen as compared to five boys on DSCG. Only one boy had good protection on both drugs.

With respect to asthmatic symptoms and anti-asthmatic medication no differences were noted between the weeks of ketotifen and DSCG treatment or during the wash-out period. No adverse reactions were noted for any of the two drugs tested.

DISCUSSION

In this study ketotifen and DSCG have shown protective effect on EIA in individual asthmatic boys, but for the whole material no significant difference against control conditions was seen. This is not in accordance with some earlier studies where DSCG (6, 10, 11) and ketotifen (5, 13) were found to offer protection against EIA,

and it is especially of interest concerning DSCG as this drug has been regarded to offer good protection against EIA. More recently, however, it has been shown that this effect is not so pronounced as was earlier thought (4) and that inhaled aerosolized DSCG was no better than pre-treatment with saline. In another recent study (9) of a group of mainly adult asthmatics, ketotifen did not prove to prevent EIA, but the patients were only given single doses of ketotifen of 1, 2 and 4 mg 2 h before exercise.

In the present study, however, the patients were pre-treated with ketotifen for 1 week before exercise and ketotifen seems to have given some protection for EIA, but must be regarded as having a limited value in this respect. This is in line with earlier reports (1, 4) where it has been pointed out that oral pre-treatment does not give any significant protection for EIA. Beta₂-agonists for inhalation still seem to be the drugs of choice in preventing post-exercise bronchoconstriction.

Great individual differences in the response to the two drugs tested were noted in this study. Similar differences have been shown in an earlier investigation (8). This might indicate that ketotifen and DSCG give protection for different populations of asthmatics. As air temperature and humidity were not standardized for the different test situations, variations in these parameters may also have influenced the results.

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