

Comparison of the Clinical Effect of Ketotifen and DSCG in Pollen-Induced Childhood Asthma

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Thirty-six children with a mean age of 8.9 years were studied with respect to the prophylactic effect and tolerance of ketotifen in comparison with disodium cromoglycate.

All had a verified deciduous tree pollen-induced asthma.

The children were stratified into two matched groups and the double-blind technique was used. The study was performed during the whole deciduous tree pollen season. Daily pollen counts were performed during the whole observation period as well as daily registrations of allergic symptoms, additional medication and pulmonary expiratory flow. No significant differences were found between the two substances tested. No adverse reactions or side effects were noted.

Key words: bronchial asthma; childhood; disodium cromoglycate; ketotifen; prophylactic treatment; tolerance.

Accepted for publication 19 October 1979

During the last decade prophylactic treatment in childhood asthma has developed to a leading therapeutic principle. Up to now the only drug available for this form of therapy has been disodium cromoglycate, DSCG. This substance has well documented clinical properties and very few side effects have been reported. Treatment with DSCG is usually successful but it has some practical limitations in paediatric practice. These are due to the short duration of the drug and the way it has to be administered, as powder by inhalation. Many children find it difficult to take it four times a day and some develop troublesome cough or even asthma after inhalation of the powder.

Recently a new drug, ketotifen (HC 20-511), with prophylactic anti-asthmatic, as well as antihistaminic, activity (6) has been introduced. It seems likely that the compound acts either directly or indirectly on the mast cells by inhibiting the c-AMP phosphodiesterase and/or the release of mediator

substances (7). However, the working mechanism is not yet known in detail and there are some indications that the *in vivo* effects of ketotifen might be more due to its antihistaminic properties than to mast cell inhibitor mechanisms (1). Ketotifen is well absorbed from the gut (3) and can be administered orally twice a day.

The aim of the present study was to compare the prophylactic effect and tolerance of ketotifen, given orally as tablets, with DSCG, inhaled in powder form, in children with birch tree pollen-induced bronchial asthma during the deciduous tree pollen season.

PATIENTS

Thirty-six children, 25 boys and 11 girls, with a mean age of 8.9 years (range 4.1-14.9 years) were studied. All were out-patients at the Paediatric Clinic, Huddinge Hospital and all had a positive history of bronchial asthma, during the deciduous tree pollen season, of at

least 2 years. Breathing disturbances were maximal from the beginning of May to the middle of June, which corresponds to the birch pollen season in the middle part of Sweden. All children had positive prick tests (Vitrum Standard Allergens), positive RAST (Phadebas, Pharmacia) and/or positive bronchial challenge for birch-tree pollen. Six patients had received six months hypo-sensitization therapy with 3-tree-mix (Allpyral) and another eight patients for 18 months, none had been treated during more than one deciduous tree pollen season. Eight children had previously had a good protective effect with DSCG, none had previously been treated with steroids. Thus, the degree of the asthma disease was not judged as severe.

All patients and parents were given full information concerning the study and gave their consent for participation. The study was approved by the Committee of Ethics at Huddinge Hospital.

METHODS

Ketotifen was given orally in a dose of 1 tablet (1.0 mg) twice a day to patients with a body weight of 30 kg or more and 1/2 tablet (0.5 mg) to patients with a body weight below 30 kg. The daily mean dose given was 52 $\mu\text{g/kg}$ body weight (range: 36–72 $\mu\text{g/kg}$). Placebo tablets for ketotifen contained lactose.

DSCG was given by inhalation (Spinhaler) in a dose of 1 capsule (20 mg) four times a day. Placebo capsules for DSCG contained lactose.

Pollen counts were made daily from the beginning of April until the middle of June using a Burkard pollen trap placed on the roof of the hospital. Hazel, alder and birch-tree pollen were identified and counted.

The forced expiratory flow was determined three times a day from the middle of April to the middle of June using an Airflometer (Glaxo Ltd) (10). At each determination the best value of three consecutive measurements was registered. Only patients scoring 10 or more airflometer-units during the run-in period were judged to be suitable for

evaluation in this respect. Fifteen and 12 patients in the ketotifen and DSCG-group respectively fulfilled this criterion.

Asthmatic symptoms were registered every day during the whole observation period on scoring-cards, using a scoring-scale from 0 to 4 during the day and 0 to 3 during the night. Thus the maximal symptom score during 24 hours could be 7 points.

Additional medication required for asthma symptoms was scored and registered every day. Each dose taken of β_2 -stimulants orally or inhaled, and theophyllines was given 1 point and steroids or ACTH were given 4 points/dose.

Symptoms of rhinoconjunctivitis during the run-in period and each 4-week period preceding the clinical controls were registered as absent, mild, moderate or severe.

Medication for rhinoconjunctivitis was registered and scored. Each dose taken of antihistamines or decongestants was given 1 point.

Determinations of haemoglobin, white blood cell count, platelets, total number of eosinophils, eosinophils in nasal smear, sedimentation rate, serum bilirubin, serum creatinine, ASAT, ALAT and alkaline phosphatase were made at regular intervals using routine laboratory techniques.

Determinations of IgE and RAST for birch-tree pollen were made, using the methods Phadebas IgE PRIST® (Pharmacia) and Phadebas RAST® (Pharmacia), respectively.

For assessment of asthma and rhinoconjunctivitis statistical analysis of contingency tables with 2I-statistic and median-test with 2I-statistic were used.

PROCEDURE

The double-blind technique was used for the two treatment alternatives:

1. Ketotifen group:
ketotifen + placebo for DSCG.
2. DSCG group:
DSCG + placebo for ketotifen.

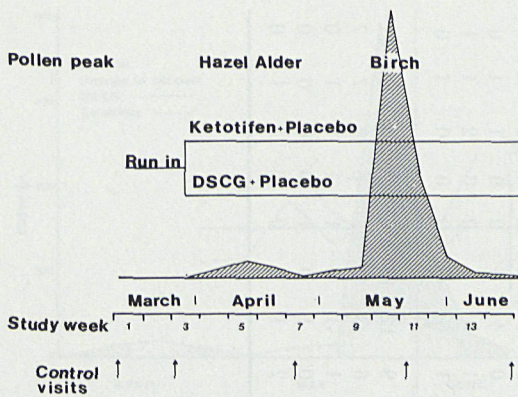


Fig. 1. Trial design for comparison of the anti-asthmatic effect of ketotifen and DSCG in two groups of children with deciduous tree pollen-induced asthma. Double-blind technique was used.

The children selected for the study were stratified into matched pairs with regard to having had hyposensitization treatment or not, severity of asthma, presence of rhinoconjunctivitis during pollen seasons, age and sex. Within the pairs, the two treatment alternatives to be compared were randomly distributed, thus forming the ketotifen and DSCG groups. As seen in Table 1 the two treatment groups were well comparable with respect to the basic data and no statistical differences between the groups were found (U-test) (5).

The study started in the middle of March, during the non-pollen season, with a 2-week run-in period. The run-in period was used to record the baseline asthmatic symptoms, medication of β_2 -stimulants and theophyllines as well as getting the patients acquainted with the registration cards and Airflowmeters. These weeks also served as a wash-out period for patients earlier on DSCG treatment. During the 2nd run-in week basic data for lung function, asthmatic symptoms and anti-asthmatic medication were obtained. The treatment period with ketotifen and DSCG started at the end of March and continued for 11 weeks during the deciduous tree pollen season until the middle of June (Fig. 1). Clinical controls and laboratory investigations were made during the observation period at five and three occasions, respectively.

RESULTS

The prophylactic effect of the two drugs tested was evaluated in terms of registered asthmatic score, additional medication taken and airflow recordings. Both ketotifen and DSCG provided protection against asthmatic symptoms during the whole deciduous tree pollen season (Table 2). Most patients in both groups had no or only slight symptoms (weekly

Table 1

Mean values $\pm$ 1 s.d. for some variables in two treatment groups of children with birch pollen-induced asthma

	Ketotifen	DSCG
No. of patients	18	18
Sex		
Boys	12	13
Girls	6	5
Age (years)	8.9 $\pm$ 2.8	8.9 $\pm$ 3.2
Height (cm)	133.1 $\pm$ 18.3	132.7 $\pm$ 21.7
Weight (kg)	29.4 $\pm$ 10.4	30.4 $\pm$ 12.4
Duration of asthma (years)	4.7 $\pm$ 3.0	4.3 $\pm$ 2.0
Hyposensitization therapy (no. of patients)	7	7

Table 2

Number of patients in relation to different degrees of asthmatic symptoms and additional medication taken for asthma complaints. Two groups of asthmatic children treated with ketotifen and DSCG were studied before (week 1-2) and during the deciduous tree pollen season. The birch pollen peak occurred during weeks 10 and 11

	Weekly score	DSCG group													Ketotifen group												
		Week													Week												
		1	2	3	4	5	6	7	8	9	10	11	12	13	1	2	3	4	5	6	7	8	9	10	11	12	13
Asthmatic symptoms	0	13	11	13	14	14	14	12	13	11	12	10	12	11	13	14	12	11	11	7	9	11	10	8	6	11	8
	1-7	2	5	4	1	1	2	2	1	5	2	5	3	4	4	3	5	5	4	9	5	2	8	10	9	4	9
	8-14	1	1	1	1	0	0	1	0	1	2	2	2	0	0	1	0	2	1	0	4	4	0	0	1	1	0
	15-21	1	1	0	2	2	2	3	3	0	0	0	0	1	1	0	1	0	0	1	0	1	0	0	2	1	1
	> 21	1	0	0	0	1	0	0	1	1	2	1	1	1	0	0	0	0	2	1	0	0	0	0	0	1	0
Additional medication for asthma	0	10	10	13	14	13	15	11	12	10	11	9	11	10	13	14	13	14	12	9	12	12	11	11	8	9	11
	1-7	4	4	2	1	2	1	3	2	6	4	5	3	5	4	2	2	3	3	6	3	3	5	6	8	7	7
	8-14	1	2	2	0	1	1	2	2	1	0	2	2	0	0	2	3	1	2	1	1	1	1	1	1	1	0
	15-21	2	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0
	> 21	1	2	1	0	2	1	2	2	1	3	2	2	2	1	0	0	0	1	2	1	2	0	0	1	1	0

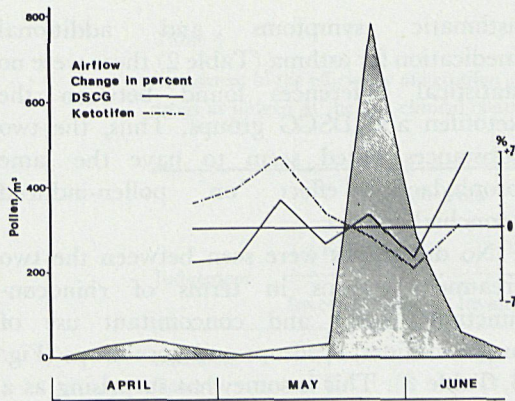


Fig. 2. Airflow recordings in the ketotifen ($n = 15$) and DSCG ($n = 12$) treated groups. Weekly mean values as percentage deviation from basic recordings during the run in period.

score interval = 1–7) even during the peak pollen period. There were no statistically significant differences between the two treatment groups tested. Additional medication for asthmatic complaints did not show any significant increase during the pollen season as compared with the basic recordings for either ketotifen or DSCG (Table 2) and there was only a small rise in the low medication score interval (weekly score = 1–7 points) during the maximal birch tree pollen period. No significant differences were found between the two drugs and their protection effect seemed to be satisfactory. In Fig. 2 the mean weekly airflow recordings are shown ($n = 27$) as percentage deviations from the basic recordings during the second week of the run-in period. During the birch pollen peak there was only a small decrease in the air flow score of 3.8% in the ketotifen group and 2.8% in the DSCG group. There were no significant differences during the deciduous tree pollen period in either the absolute or the percentage changes to the baseline values, neither within the groups nor between the two groups (2-way analysis of variance with repeated measurements) (13).

Rhinoconjunctival symptoms during the treatment period were recorded at each control visit and the recordings covered the

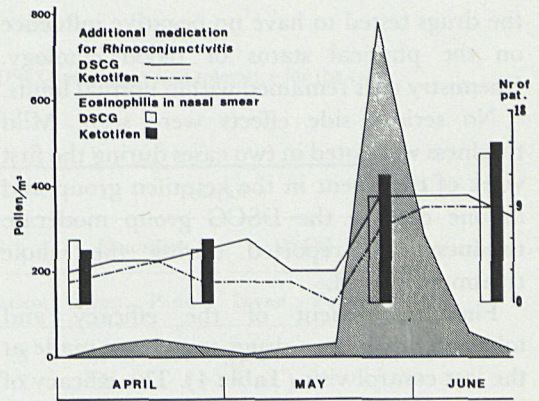


Fig. 3. Number of patients in the ketotifen and DSCG treated groups who had taken symptomatic medication for rhinoconjunctivitis. Included are the number of patients in both groups who had a raised number of eosinophils in nasal smears, found at the clinical controls.

preceding 4-week period. Compared with the symptoms during the run-in period, there was a mild to moderate rise during the peak deciduous pollen season (Table 3) indicating that the drugs tested did not have a full protective effect in this respect. No differences were found between ketotifen and DSCG. The additional medication score for rhinoconjunctivitis showed the same pattern (Fig. 3) with a moderate increase during the peak pollen period. Eosinophils in nasal smears were raised markedly in both groups during the peak pollen period. There was no difference between the two groups tested (Fig. 3).

Clinical control and laboratory tests showed

Table 3

Number of patients in the two groups studied reporting symptoms of rhinoconjunctivitis at the control visits. Control number 4 was during the birch pollen peak and at control 5 the grass pollen period had started.

Control no.	Ketotifen				DSCG			
	2	3	4	5	2	3	4	5
Absent	17	11	6	6	15	13	6	7
Mild	1	5	7	8	2	4	5	8
Moderate	0	1	5	3	1	1	7	2
Severe	0	1	0	1	0	0	0	1

the drugs tested to have no negative influence on the physical status or blood cytology. Chemistry tests remained within normal limits.

No serious side effects were seen. Mild tiredness was noted in two cases during the first week of treatment in the ketotifen group and in one case in the DSCG group moderate tiredness was reported during the whole treatment period.

Final assessment of the efficacy and tolerance of the two drugs tested was made at the last control visit (Table 4). The efficacy of both drugs was judged as excellent or good by almost all patients and poor in only one case being treated with ketotifen. The tolerance was judged as excellent for both drugs in all but one case in each group. There were no significant differences between the two treatment alternatives in terms of efficacy or tolerance.

DISCUSSION

In this study, ketotifen and DSCG have shown the same protective effect on pollen-induced asthma. In the ketotifen group only a few children had moderate or pronounced asthmatic symptoms (weekly score ≥ 8) during the whole period (Table 2). During the 2 weeks of maximal birch pollen exposition there was a small change from no symptom level to slight symptoms (weekly score = 1–7) but there still was no rise in the highest symptom score intervals. There was no correlation between the degree of asthmatic symptoms and given dose of ketotifen expressed in terms of $\mu\text{g/kg}$ body weight.

Up to 56% of the patients had to take additional medication for asthmatic symptoms during the birch pollen peak as compared with 22% during the 2nd run-in week (Table 2). However, almost the whole rise in medical consumption was located to the low medication score interval (mean weekly score = 1–7) so the asthmatic complaints must be regarded as slight.

Even if the DSCG group had a few cases in the higher score intervals with regard to

asthmatic symptoms and additional medication for asthma (Table 2) there were no statistical differences found between the ketotifen and DSCG groups. Thus, the two substances tested seem to have the same prophylactic effect on pollen-induced bronchial asthma.

No differences were seen between the two treatment groups in terms of rhinoconjunctivitis score and concomitant use of antihistamines, eyedrops and nose-drops (Fig. 3, Table 3). This is somewhat surprising as a difference in favour of ketotifen was expected from its documented good antihistaminic properties (6).

No serious drug related adverse reactions were seen. Mild tiredness was only noted initially in two cases treated with ketotifen.

In one case the tolerance for ketotifen was judged as good instead of excellent (Table 4). This patient had moderate coughing in connection with placebo inhalation and following a period of infection with asthmatic symptoms the patient stopped taking not only placebo but also ketotifen until asthmatic symptoms occurred during the birch pollen peak. Following reinstitution of ketotifen treatment, improvement was noted. In this case even the overall efficacy of treatment was judged as poor, which to a great extent may be due to the cessation of the treatment during the most critical period of the study.

In one case the tolerance for DSCG was judged fair (Table 4) probably due to repeated ENT-infections with asthmatic symptoms. DSCG and ketotifen placebo was only taken for short periods during the ENT-infections, explaining the slight therapeutic efficacy and fair tolerance.

In earlier studies it has been demonstrated in adult asthmatics that ketotifen provides good protection against bronchoconstriction induced by allergens (2, 4, 9), histamine and exercise (2, 14). The positive effect against allergen-induced bronchoconstriction does not seem to differ from that of DSCG (9). On the contrary, in a more recent study (12) bronchial challenge with cat fur allergen in asthmatic

Table 4

Assessment of the efficiency of ketotifen and DSCG treatment and tolerance for the two drugs as judged at the last clinical control

Judgement	Efficiency				Tolerance			
	Ketotifen		DSCG		Ketotifen		DSCG	
	Invest.*	Patient	Invest.	Patient	Invest.	Patient	Invest.	Patient
Excellent	11	13	12	13	17	17	17	17
Good	6	3	3	2	1	1	0	0
Slight	0	1	3	3	0	0	1	1
Poor	1	1	0	0	0	0	0	0

*Invest., investigator.

children induced bronchospasm that was blocked with DSCG but not with ketotifen. It is debatable whether these divergent results might be explained by different doses and duration of ketotifen therapy prior to bronchial challenge.

In two clinical investigations (8, 11) with double-blind cross-over technique, ketotifen did not show to have any significant protective effect in children with perennial bronchial asthma, as compared with placebo, but there is no information on whether they were sensitized for pollen or not. In one study (11) the presence of pollen may have influenced the results. No pollen counts were made. As the present study was made in pollen-sensitized children during the pollen period the results are not fully comparable with those of the previous clinical investigations. As birch-tree pollen in Sweden causes pronounced allergic reactions in sensitized individuals within a short period of time, it can serve as a useful clinical model for studying allergen-induced bronchial asthma. The pollen peak during the period studied was very high (max. 5,483 pollen/m³ a day) so the degree of allergen exposure must be regarded as sufficient for provoking allergic symptoms.

In this study, ketotifen and DSCG have shown the same effect on childhood pollen-induced bronchial asthma and no side effects

of clinical importance were seen. Because of the easy route of administration, ketotifen might be a good alternative in the prophylactic treatment of children with pollen-induced bronchial asthma.

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