

The Protective Effect of a New Agent, Ketotifen Syrup, in the Treatment of Childhood Asthma

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Twenty-two children with perennial extrinsic allergic asthma participated in a double-blinded, controlled, cross-over study of Ketotifen syrup during a 2 x 6-week period. The placebo was identical with the active drug in taste, colour, and consistency. The dosage level was, on weight basis, a little higher than the standard dosage for adults.

The double-blinded investigation was supplemented with a 12-week open study of the tolerance for Ketotifen. This study also involved 22 patients, 12 new ones, and 10 from the double-blinded study.

The study showed Ketotifen to have no effect on changes in lung function (peak flow), on reduction in frequency of asthmatic attacks, or on consumption of additional medicine.

The tolerance for Ketotifen was good, but physicians are advised to watch for increases in weight and decreases in blood pressure during tests on children which involve higher dosage levels.

Key words: asthma; children; Ketotifen syrup; prophylactic treatment; tolerance.

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Ketotifen, a cycloheptathiophene derivative, was synthesized in an attempt to produce a new and better antihistamine. Animal experiments (7) have shown Ketotifen to have a stabilizing effect on the mast cells, and also to have a regular antihistamine effect. Several investigations on adults (1, 2, 3, 4, 6, 8) suggest that this drug has a prophylactic effect on bronchial asthma. As yet, there have been no publications on the effect of Ketotifen on children. The Galenic syrup form became available for clinical testing in 1977, and was used in the present investigation to test the effect of Ketotifen on children with bronchial asthma.

MATERIAL AND METHODS

Thirty-four children, half from each of the pediatric departments at the county hospitals

in Ålborg and Viborg, Denmark, participated in an investigation to test the prophylactic effect of Ketotifen.

The prophylactic effect was evaluated in a controlled, double-blinded, cross-over study of 22 children covering a 2 x 6 weeks' period. The placebo was identical with the active drug in taste, colour, and consistency. The dosage level was comparable to that used in adult studies (0.04 mg/kg/day). The parents and the children were informed, both verbally and in writing, about the investigation, including the fact that an inactive substance would be used at some time during the treatment period.

The patients were 12 boys and 10 girls having a mean age of 10.2 years, and a mean duration of asthma symptoms of 6.7 years. All patients had extrinsic asthma without seasonal variation, and were multi-allergics,

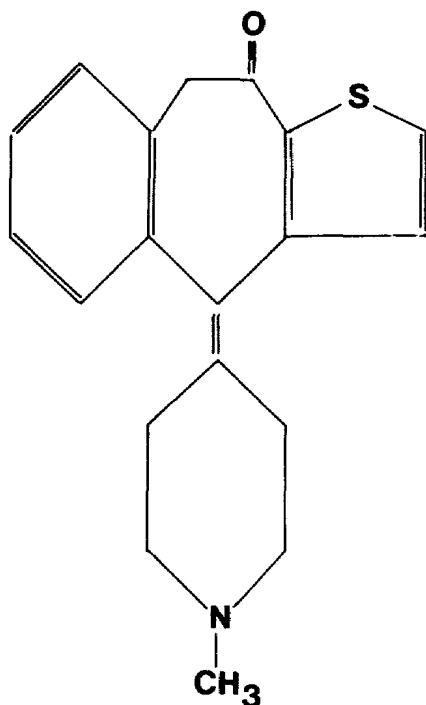


Fig. 1. Ketotifen. A cycloheptathiophene derivative.

having a positive reaction to a mean of 4.5 allergens. Most of them had increased IgE, eosinophilia, and associated allergic diseases. Children with chronic gastro-intestinal, kidney and liver diseases were excluded from the study. The patients were not allowed to take disodium cromoglycate during the investigation, and were given beclomethasone dipropionate only if other forms of therapy failed. Patients who were hyposensitized were required to remain on a maintenance dosage level.

Clinical recordings included: the frequency and duration of asthma attacks, the occurrence of exercise-induced asthma, peak expiratory flow rate (PEFR), measured in the mornings and evenings before taking Ketotifen, and the use of additional medicine. Every 3rd week the patients were

clinically examined, which included checking blood pressure, weight, heart rate, and subjective reports by both patient and physician on the effect of the drug, if any. The patients delivered monthly reports containing the registered data. Before and after each 6-week treatment period, haemoglobin, white cell count, white cell differential, platelet count, se-aspartataminotransferase, and blood urea nitrogen were checked. The patients' subjective side effects were also registered at each clinical examination.

The tolerance for Ketotifen covering a 12-week period was investigated in 22 patients, 12 new ones, and the 10 from the blind study who received Ketotifen during the 2nd 6-week period. Furthermore, six of these patients got increased doses of 20–40%. The patients were clinically examined after 6 and 12 weeks, at which times the same subjective and objective parameters were recorded as in the blind study.

RESULTS

Twenty-one patients in the blind study, and all 22 patients in the open tolerance study completed the entire treatment period. One patient was dropped from the study because of progressive asthma from the 5th to the 7th treatment week. This patient received placebo from the 6th week.

Fig. 2 shows the mean evening PEFR values taken for single patients in the placebo period (on the y-axis), and the Ketotifen period (on the x-axis). The identity line indicates equal mean PEFRs for the two periods. The data points are evenly distributed about this line, showing no difference between the Ketotifen and placebo effects ($P=0.85$). To expose systematic errors in one of the two periods, for example, poor initial PEFR measuring technique, or changes in the use of medicine just prior to the experiment, the data points also indicate whether the patient received the active or the inactive substance during the first 6-week period. The treatment order had no effect on

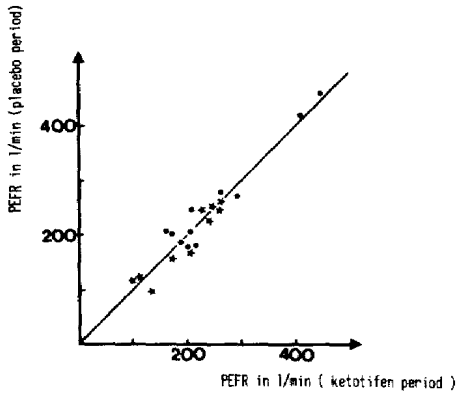


Fig. 2. Evening peak expiratory flow rate (PEFR in l/min) in placebo and Ketotifen period. Ketotifen period first: ●, and placebo period first: ★.

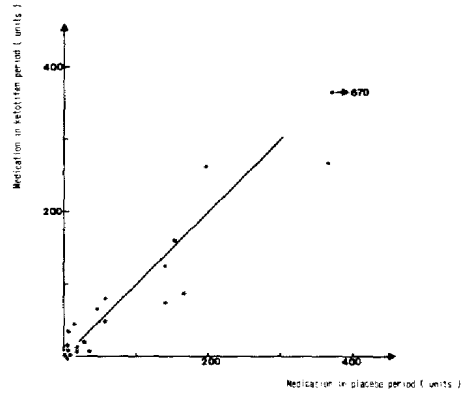


Fig. 3. Additional medication in placebo and Ketotifen period (units, see Table 1). Ketotifen period first: ●, and placebo period first: ★.

the results. The curve for the mean morning PEFR values is not given here, but resembles very closely the evening PEFR curve in Fig. 2.

Table 1 gives approximate equivalent doses of the medicine used, transformed to units by a scoring system based on equalizing daily maintenance dosage levels of various types of medicine. Prednisone and hydrocortisone were given only for treatment of status asthmaticus.

Fig. 3 compares the use of additional medicine in the Ketotifen period (y-axis), and in the placebo period (x-axis). The use of additional medicine was measured in units as defined in Table 1. Four patients had a clearly greater use of additional medicine during the placebo period than during the Ketotifen period. Three of them, however, also had a higher PEFR during the placebo period, suggesting they were "overdosed"

Table 1
Equivalent potency (units) for different drugs

Drug	Dose	Equivalent potency (units)
Terbutaline aerosol	1 puff (0.25 mg)	1
Terbutaline tablet	5 mg	4
Terbutaline elixir	2.5 mg	2
Terbutaline inj.	1 injection	2
Salbutamol aerosol	1 puff (0.10 mg)	1
Salbutamol tablet	4 mg	4
Salbutamol elixir	2 mg	2
Aminophylline supp.	100 mg	2
Beclomethasone dipropionate	1 puff (0.05 mg)	1
Prednisone tablet	1 mg	1
Hydrocortisone inj.	4 mg	1
Proxyphylline tablet	200 mg	2
Proxyphylline inj.	1 injection	2
Epinephrine inj.	1 injection	2

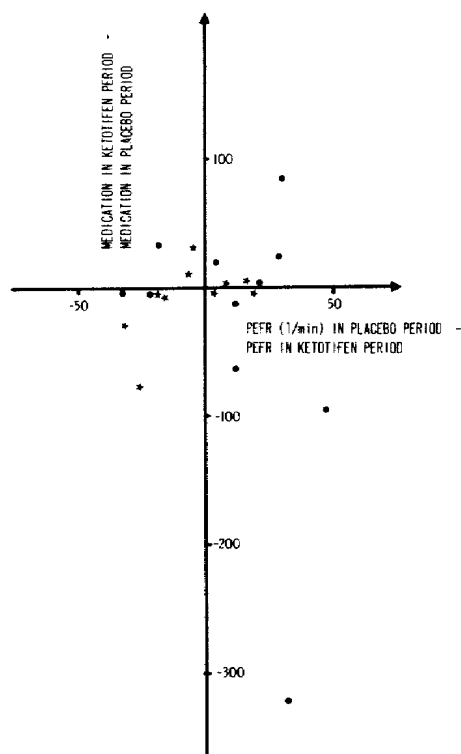


Fig. 4. Difference in medication versus difference in lung function (PEFR in l/min) in relation to Ketotifen and placebo period. Ketotifen period first: ●, and placebo period first: ★.

(3–6 o'clock quadrant, Fig. 4). Since some patients did better during the placebo period than during the Ketotifen period, there was no effect in the use of additional medicine ($P=0.30$).

Fig. 4 shows a simultaneous comparison of the use of additional medicine (y-axis) and PEFR values (x-axis) in both placebo and Ketotifen periods. If Ketotifen were effective, the data points should fall in the 6–9 o'clock quadrant, however, only two points are clearly located here which shows that Ketotifen had no effect ($P=0.75$).

There was no reduction in attack frequency, or change in subjective reports of improvement with the active substance.

Side effects

Two children had temporarily slight initial sedation effects, but one of these patients had similar symptoms during the placebo period. Two had stomach aches during the 1st week of treatment. One of these patients also had nausea and slight fever. A single patient had nausea and vomiting for 1 week beginning 4 days after the start of the treatment. There was a net weight increase (Ketotifen period minus placebo period) of 0.62 kg, which is near significance ($P=0.07$). This was supported by a similar weight increase tendency in the open investigation. There was a slight but significant fall in the systolic blood pressure in the blind study (approx. 5 mmHg, $P=0.02$). In the open tolerance study, there was also a slight but significant fall in both systolic and diastolic blood pressure after the 6th week of treatment (approx. 5 mmHg, $P<0.05$). There was no change in heart rate, and no influence of the haematological parameters.

DISCUSSION

We could not demonstrate any effect of Ketotifen in this double-blinded investigation on children. Only a few blind studies have been made on adults with bronchial asthma (3, 4, 6, 8). Of these, only one (3) used a placebo control. The others used clemastine, but all demonstrated an effect of Ketotifen.

The adult doses were 2 mg/day. The children's doses were 0.04 mg/kg/day (max. 2 mg), and were thus comparable; however, the children's doses were a little higher, measured on a weight basis. Some authors (4, 6, 8), during blind experiments, changed from 2 mg to 4 mg/day without producing greater clinical effects.

As in other studies, we have shown a reasonably good tolerance for Ketotifen. However, we suggest that physicians pay attention to blood pressure and weight, es-

pecially in investigations using higher dosage levels for children. We have interpreted the weight increase as a side effect since there was no main effect of Ketotifen on asthma. In a single investigation on adults (5) a mean weight increase of 1.5 kg was shown, but only when double the standard dose (4 mg/day) was used. Six patients in the open investigation got dosage levels that were increased by 20–40% in the latter 6 weeks of the treatment period. None of these patients had subjective side effects from the increased doses, and their blood pressure and weight changes were comparable with those found in the other patients.

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