

Multicenter study with ketotifen (Zaditen) oral drop solution in the treatment of wheezy children aged 6 months to 3 years

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One hundred and seven chronically wheezing infants, aged 6 months to 3 years, completed a double-blind placebo controlled multicenter study. After a two-week baseline period the patients were randomized into two groups receiving twice daily either ketotifen or placebo for a period of 12 weeks. The ketotifen dosage was 0.5 mg for children younger than one year and 1 mg for the older. During the 12-week treatment period the patients from the two groups demonstrated gradual improvement of the disease severity parameters, as compared with the baseline period. The amelioration was more marked in the ketotifen treated patients and during the 0–4, and 4–8 weeks of treatment a significant decrease was achieved in the percentage of days with a cough ($p < 0.04$) and in the number of wheezing episodes ($p = 0.02$). Moreover, a 50% reduction of the days and nights with cough and in the number of wheezing episodes occurred earlier in the ketotifen than in the placebo treated patients, i.e. after 1.2 vs 4.6; 4.4 vs 8.6 and 5.2 vs 7.2 weeks, respectively. It should be stressed that the amelioration of the asthmatic morbidity in the ketotifen group was achieved with a significantly reduced need for the concomitant use of bronchodilators. The principal side effects observed were weight gain and transient sedation. It is concluded that ketotifen may be effective in the amelioration of asthma associated symptomatology and acceleration in the natural tendency for improvement in chronic wheezing infants.

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Many infants and children during the first years of life, experience recurrent wheezy episodes frequently induced by viral infections and in some of these patients mild chronic symptoms persist during the intervals between the acute exacerbations (1, 2).

The management of such wheezing infants and young children has been unsatisfactory and there is controversy concerning the efficacy of drug therapy for prevention of recurrent acute episodes and amelioration of chronic symptoms. Nebulized sodium cromoglycate has been recommended, al-

though the results reported are not as satisfactory as in older children (3, 4). In severe cases, inhaled corticosteroids are proposed although reports of their efficacy are controversial and their administration is associated with technical difficulties (3, 5–7). Theophylline, although more easily administered than the inhalation therapy, is frequently associated with serious side effects and is not well tolerated in this age group (8).

Ketotifen, an anti-allergic drug with antihistaminic effects, is widely used in the prophylaxis of asthma (9). This preparation is thought to have a wide spectrum of activity. It has been shown that ketotifen stabilizes mast cells and platelets antagonizes PAF, optimizes beta-receptor function and blocks H1-histamine receptors (10–11). In addition, it has been suggested that ketotifen has the

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capability to ameliorate pulmonary pathology irrespective of the initiating stimulus (12). In several studies encouraging results of the use of ketotifen in wheezing infants and young asthmatic children has been reported (13–18), while in others no efficacy was demonstrated (19–23).

The present study was undertaken to further evaluate the prophylactic activity of ketotifen oral drops solution in wheezing infants in a double blind randomized design.

Patients and methods

The study involved 5 pediatric centers in Israel and was conducted in a randomized, double-blind, parallel group design. The patients were recruited between January 1989 until the end of July 1989. It should be noted however that the majority of the children (79%) were enrolled during the winter months of January–March. Included were children aged 4 months to 3 years who were referred to the outpatient asthmatic clinics of the centers participating in the study with a history of three or more wheezing episodes during the 12 weeks preceeding the study. A wheezing episode was defined as an episode of dyspnea and cough associated with expiratory wheezing on auscultation which lasted 24 h or more and which necessitated referral to the patient's family physician or the hospital emergency room. Infants who were treated with sodium cromoglycate or ketotifen for 4 weeks or more during the 2 months preceeding the trial, or who had a history of congenital or chronic lung disease such as cystic fibrosis, bronchopulmonary dysplasia, etc were excluded.

An effort was made to conduct the study in accordance with the suggestions of the American Academy of Allergy and Immunology Task Force on Guidelines for Clinical Investigating of Non-bronchodilator Asthmatic Drugs (24): a) use of an homogeneous population in terms of the severity and type of medication used to control symptoms; b) use of the reduction of concomitant medications as an index of severity; c) daily PEF measurements; d) periodic spirometry.

Because of the difficulties encountered to meet the last two suggestions in studies in very young children, namely the measurement of lung functions, a scoring systems was used as an index of severity for monitoring the various parameters associated with asthma symptomatology.

The study was approved by the hospital ethics committee and informed written parental consent was obtained.

The format of the study:

- 1) A 2-week baseline period during which the patients received only his/her usual medications necessary for control of asthmatic symptoms.
- 2) A 12-week treatment period during which the patient received at random ketotifen oral drop solution or placebo. The ketotifen dose was 0.5 mg twice daily for patients aged 1 year or less and 1 mg twice daily for the older children.
- 3) An 8-week post treatment period during which no trial drugs were administered. The patients were assessed as in the 12-week treatment period.
- 4) Optional extended post treatment follow-up of 10 additional months (until the end of a one year period after the completion of the 3-month active treatment).

The patients were allowed to use inhaled beta-2 agonists (terbutaline administered by home aerosol apparatus), theophylline and oral steroids if indicated to control their asthmatic symptomatology.

The children were examined at scheduled visits – at the end of the 12-week run-in period, and at 4-week intervals during the following 20 weeks (12 week treatment period and 8 week post treatment follow up). The patients who agreed to participate in the extended post treatment follow up were examined at intervals of 2 or 3 months. In addition, parents were told to bring the patients to the hospital clinics in the event of exacerbation of symptoms.

During the run-in period and the following 20 weeks of the trial (12-week treatment and 8-week post-treatment follow up), the parents were requested to complete a diary card which included information on wheezing, dyspnea, day and night cough and nasal discharge. Symptoms were scored according to a scale of 0–2; 0 = no symptoms; 1 = mild to moderate and 2 = severe symptoms. Likewise, the use of concomitant medications and occurrence of side effects were recorded.

Statistical methods

The significance of differences between means for all parameters was tested with the use of a Student's two-sample t-test under the assumption that the scores are independent observations from normally distributed populations. Comparison of the number of days with asthmatic symptoms between two groups of patients at the same period, was performed with a Student's t-test for unpaired data. Comparison of data within each of the two study groups to the baseline was performed by means of the Student's t-test for paired data. Com-

Table 1. Background information of the study population

	Ketotifen Mean $\pm$ SD	Placebo Mean $\pm$ SD
Study population		
No. of children	53	55
Mean age (months: mo.)	16 $\pm$ 7 mo.	17 $\pm$ 9.5 mo.
Sex (male: female)	33:20	36:19
Allergy in family	54%	41%
Height (cm)	78.0 $\pm$ 9.2	78.0 $\pm$ 9.2
Weight (kg)	10.6 $\pm$ 2.5	10.3 $\pm$ 2.4
Asthma severity during the preceeding 3 months		
No. wheezing episodes	4.4 $\pm$ 2.4	4.2 $\pm$ 2.3
No. of ER visits*	1.5 $\pm$ 1.3	1.3 $\pm$ 1.3
No. of hospitalizations	0.6 $\pm$ 1.0	0.5 $\pm$ 1.2
Drug usage (weeks)		
Beta-2 agonists	6.1 $\pm$ 5.0	5.6 $\pm$ 4.3
Theophylline	2.8 $\pm$ 4.4	2.8 $\pm$ 3.5
Oral steroids	0.7 $\pm$ 0.9	1.0 $\pm$ 1.5

* ER – Emergency room. No statistically significant differences were found in any of the parameters evaluated.

parison of the number of patients in each period to the baseline was tested by the means of the Chi-square test or Fischer's Exact test 2 $\times$ 2 tables (qualitative data). A P-value of less than 5% was considered to indicate significance.

Results

Initially, 117 patients were included but only 108 were available for the final evaluation. Nine patients were excluded because of non-compliance or incomplete data, especially daily diary records. The mean age ($\pm$ SD) of the patients at the time of entry into the study was 1 year and 5 months ($\pm$ 9.6 months), with range of 6 months to 3 years.

The ketotifen and the placebo-treated groups of patients at inclusion to the study were comparable in terms of: age, sex, height, weight and a history of allergy in the family (Table 1). There were no significant differences in the asthmatic severity and morbidity between the two treatment groups during the three months preceding the inclusion to the trial in all the parameters evaluated, *i.e.* the number of wheezing episodes, emergency room visits and hospitalization for asthma and anti-asthmatic drug usage, (beta-2 agonists, theophylline and oral corticosteroids) (Table 1).

Similarly, no significant differences between the two study groups were observed during the baseline period in any of the evaluated parameters except for the number of wheezing episodes (Table 2).

Table 2. Asthmatic severity during the two weeks baseline period

	Ketotifen Mean $\pm$ SD	Placebo Mean $\pm$ SD	P
Number of			
Wheezing episodes	2.8 $\pm$ 2.0	2.1 $\pm$ 1.3	0.03
Mean % of days with			
Day cough	55.0 $\pm$ 31.4	60.1 $\pm$ 32.9	NS
Night cough	38.0 $\pm$ 30.4	45.3 $\pm$ 32.5	NS
Wheezing	42.1 $\pm$ 31.5	43.6 $\pm$ 35.6	NS
Running nose	58.6 $\pm$ 37.3	49.4 $\pm$ 34.8	NS
Mean % patients with			
Theophylline usage	42.0	27.0	NS
Beta-2 agonists usage	81.0	73.0	NS
Corticosteroids usage	4.0	12.0	NS

Asthmatic symptomatology

The percentage of days with day cough, night cough and wheezing (Table 3) and the number of wheezing episodes (Fig. 1, top) in both study groups decreased gradually over the 12 weeks of treatment and the 8-week post-treatment and were significantly lower than during the baseline period. The decline in the severity of symptoms seen in the children treated with ketotifen was greater than in those receiving placebo, and for some symptoms this trend reached statistical significance. During the first two treatment periods (0–4 and 4–8 weeks), the percentage of days with day cough (Table 3) and the number of wheezing episodes (Fig. 1, top) in the ketotifen treated patient was significantly lower than in the children from the placebo group, $p < 0.04$ and $p = 0.02$ respectively. Furthermore, amelioration of the asthmatic symptomatology, as reflected by a 50% reduction in the number of wheezing episodes and the number of days with day and night cough was achieved earlier in the ketotifen-treated group as compared to the

Table 3. Asthmatic symptomatology (mean percent of days)

Weeks:	Baseline		Treatment period		Post treatment	
	–2–0	0–4	4–8	8–12	12–16	16–20
Day Cough						
Ketotifen	55	34*	23	23	24	16
Placebo	60	46*	35	28	28	23
Night Cough						
Ketotifen	38	25	17	17	18	12
Placebo	45	29	24	21	21	18
Wheezing						
Ketotifen	42	31	20	16	17	10
Placebo	44	35	20	22	20	19

$p < 0.05$ for all parameters in comparison to baseline. * $p < 0.05$

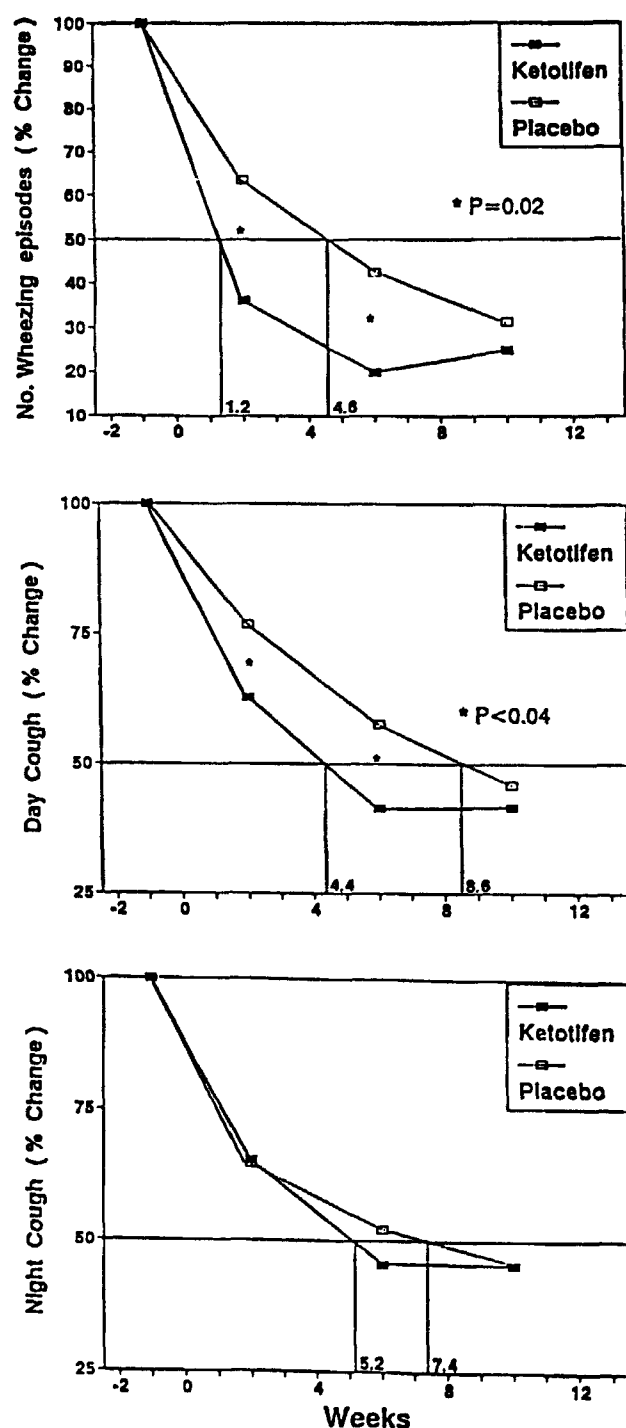


Fig. 1. Change (percent) from the baseline. Number of wheezing episodes (top). Number of days with day cough (middle). Number of days with night cough (bottom).

placebo treated patients: 1.2 vs 4.6; 4.4 vs 8.6 and 5.2 vs 7.2 weeks respectively (Fig. 1). No significant difference in the frequency of the night cough between the two groups was observed during any of the study periods.

A decrease in the number of days in which parents recorded a "running nose" during the study,

compared with the baseline period was similar in both groups (data not shown).

Use of anti-asthmatic medications

During the baseline period, 42% of ketotifen and 27% of placebo-treated patients used theophylline. The need for this declined gradually in both groups throughout the study. However, the percentage of children who needed to use theophylline was significantly lower in the ketotifen group from the 4–8 week treatment period until the end of the study, compared with the baseline period ($p<0.02$ – <0.001) (Table 4).

The percentage of patients who needed administration of beta-2 agonists decreased gradually in both groups of patients. The reduction in the use of this drug as compared to the baseline, was statistically significant in the ketotifen treated patients from the 4–8-week period ($p=0.004$), whilst in the placebo group a significant decrease was achieved from the 8–12 week period. (Table 4). The concomitant use of oral corticosteroids was low in both groups and no significant differences were observed between the patient treated with ketotifen and placebo (Table 4).

Global evaluation

The overall evaluation by parents and physicians in terms of illness severity and study efficacy during each of the study periods and at the end of the trial in comparison with the baseline period revealed progressive, but similar, improvement in both groups with one exception: during the first treatment period (0–4 weeks), the physicians scoring

Table 4. Use of additional anti-asthmatic drugs; percent of patients

	Baseline		Treatment period		Post treatment	
Weeks:	-2-0	0-4	4-8	8-12	12-16	16-20
Theophylline						
Ketotifen	42	24	19	15	16	10
P =			0.02	0.01	0.01	0.001
Placebo	27	23	19	13	17	15
Beta-2 agonists						
Ketotifen	81	67	52	53	49	42
P =			0.004	0.005	0.002	0.0001
Placebo	73	76	56	49	47	46
P =				0.02	0.01	0.02
Corticosteroids						
Ketotifen	4	4	10	6	4	4
Placebo	12	13	2	8	13	8

P = Comparison between the number of patients in each period to baseline. If not noted, the P value was not significant.

Table 5. One year post treatment follow-up (mean $\pm$ SD)

	Ketotifen (n = 19)	Placebo (n = 14)
No. of wheezing episodes	6.8 $\pm$ 5.1	7.27 $\pm$ 9.42
Days with asthmatic symptomatology	33.5 $\pm$ 22.7	33.0 $\pm$ 18.1
Days with drug usage		
Beta 2 agonists	32.8 $\pm$ 28.6	31.5 $\pm$ 24.3
Theophylline	7.0 $\pm$ 11.0	28.7 $\pm$ 49.3
Oral steroids	2.0 $\pm$ 4.3	3.8 $\pm$ 8.1
Days with runny nose	56.0 $\pm$ 46.0	39.7 $\pm$ 29.1

No significant differences were found in any of the parameters.

for the drug efficacy was significantly higher in the ketotifen than in the placebo group of patients ($p=0.002$) (data not shown).

Side effects

The children in the ketotifen-treated group gained significantly more weight during the 12-week treatment period, than those in the placebo-treated patients, mean $\pm$ SD 1110 $\pm$ 670 gr and 820 $\pm$ 720 gr respectively ($p=0.04$). Similarly, during this period the ketotifen-treated subjects gained significantly more height than the placebo-treated children, mean $\pm$ SD of 4.2 $\pm$ 2 cm vs 3.3 $\pm$ 1.7 cm respectively ($p=0.04$).

During the first 4-week treatment period somnolence was observed in significantly more children treated with ketotifen than in the patients receiving placebo, 35% and 15% respectively ($p=0.004$). In the remaining study periods, however, this side effect was minimal in the two groups.

The mean amounts of drugs taken were 91.3% and 94.4% of those prescribed in the ketotifen- and placebo-treated patients respectively, measured by the amount returned at each visit.

Post study follow-up

Thirty-three patients, 19 from the ketotifen and 14 from the placebo group, agreed to a 10-month post treatment follow-up. The analysis of the results for these patients was done in consideration of the 12-month follow-up after completion of the treatment: 2 months (8 weeks) post-treatment and 10 months post-study follow-up periods. No difference between the two groups of patients was found in any of the parameters evaluated with regard to the wheezing-associated morbidity and severity, as detailed in Table 5. During the one-year post treatment follow-up, a similar weight gain was observed in both groups of children.

Discussion

The present study demonstrated less asthmatic symptoms in infants with recurrent wheezing, treated during a period of 12 weeks, either by ketotifen or placebo, as compared to the morbidity observed throughout the pre-treatment baseline period. The amelioration tended to be more marked in the ketotifen treated patients. The children from the ketotifen group had a significantly decreased percentage of days with day cough and fewer numbers of wheezing episodes during the 0–4- and 4–8-week study periods than the placebo-treated children. In addition, a 50% reduction in diurnal and nocturnal cough and the number of wheezing episodes was achieved earlier in the ketotifen group than in the placebo-treated patients. It should be stressed that these results were achieved in the ketotifen group despite significantly reduced use of bronchodilators than in the placebo group.

The relatively favorable results observed in the children who received placebo is not surprising as this group was, in fact, a "bronchodilator-" rather than a "placebo-"treated group. The overall trend to improve symptom scores during the study period may reflect some placebo effect, but also the non-specific benefit associated with close supervision in the context of a clinical trial (25). It is generally accepted that the wheezy infants and children tend to outgrow his symptoms with increasing age, as part of the natural history of the disease (2, 26, 27). In addition, there is a seasonal reduction in asthmatic morbidity in infants exists during the summer as opposed to the winter months, most probably related to viral-induced respiratory infection.

The result of the present study in many aspects are in accordance with those of the multicenter trial in Canadian asthmatic children, aged 7–7.7 years (22). In a previous study (17) we observed a similarly favourable effect of ketotifen on the asthmatic morbidity in small groups of children aged 1–3 years, as has been reported by others (13–16, 18). Several controlled trials, however, have failed to demonstrate a response of ketotifen in pediatric asthma (19–23). The discrepancies between the various studies may be related to differences in the methods and designs used.

The side effects observed in the present study were similar to those previously reported (9, 17, 19), *i.e.* somnolence at the start of therapy, but disappearing afterwards, and increased weight gain.

The management of wheezing asthmatic children under the age of 3 years is difficult and controversial, particularly in infants who require pro-

phylactic treatment (3, 7). Inhalation therapies are associated with technical difficulties and low compliance. The use of theophylline as an alternative for oral therapy is associated with a high incidence of undesirable side effects, narrow blood therapeutic levels and need for monitoring the serum concentrations (8). We have demonstrated in this study that ketotifen administered in oral drop solution when used in chronically wheezing infants was associated with amelioration of the severity of the asthmatic morbidity and acceleration of the natural tendency for improvement of asthma in infants. These observations, in addition to the safety, tolerability and ease of administration suggested that ketotifen oral drops solution could be considered in the management of infants with recurrent wheezing.

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