

Efficacy and tolerability of Ketotifen in Nepalese asthmatic children: a clinical study

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Abstract

Objective To assess the efficacy of Ketotifen in asthmatic children and to record its adverse effects, if any.

Design Prospective clinical trial. **Setting** Pediatric asthma follow up clinic of a teaching hospital. **Participants** 23 asthmatic children between 3 and 15 years; 100% completed the trial on full protocol. **Interventions** Ketotifen 1mg (adjusted according to body weight, 50 mcg/kg/dose) orally twice daily for 9 months.

Main Outcome measures Primary outcome: Decrease in frequency of asthmatic attacks and severity of exacerbations with improvements in peak expiratory flow rates (PEFR). Other measures included decrease in bronchodilator requirement, steroid doses and parental perception regarding patient quality of life.

Results 34.78% children were symptom free by the end of 2nd 3 months and 65.21% had no further attack by the end of 3rd 3 months of Ketotifen prophylaxis. Those children with activity and sleep 'affected' (8.69%) and 'may be affected' (30.43%) together improved to 'may be affected' group (21.73%) by the end of 2nd 3 months and further reduced to 8.69% by the conclusion of 3rd 3 months. The duration of exacerbations was reduced in the remaining cases. Variability of PEFR decreased from 26.08% to 8.69% of children after the 3rd 3 months of Ketotifen prophylaxis. No significant adverse effect of therapy was observed during the study.

Conclusion Oral Ketotifen is effective and well tolerated for use in prophylactic treatment of bronchial asthma in children.

Key Words: Ketotifen, Asthma, Prophylaxis, Efficacy.

Asthmatic attacks are distressing to children and parents alike and are responsible for many school absences and non-participation in sports. Its underdiagnosis and undertreatment notably, has been responsible for much absences from school¹. As 'the management of asthma is to keep ahead of wheezing'^{1,2}, the need for effective preventer-therapy and decreasing excessive reliance on beta agonist have turned the balance of opinion. Studies^{3,4} have indicated that patient compliance is greater and more acceptable to parents when medications are given orally than by inhalation in asthma therapy. Ketotifen⁵⁻⁸ is an orally active prophylactic agent for the management of bronchial asthma and allergic disorders⁹. It is a benzocycloheptathiophene derivative¹⁰ with antihistaminic and antianaphylactic activity¹¹. Favourable results have been reported from its extensive trials in asthmatic adults¹²⁻¹⁷ and children^{18,19} worldwide, including in Nepal²⁰.

The present study was done with the following chief objectives:

- (i) to assess the efficacy of Ketotifen in asthmatic children attending the pediatric asthma follow-up clinic of Kathmandu Medical College Teaching Hospital, and

- (ii) To enlist its adverse effects, if any.

Materials and methods

Asthmatic children attending the paediatric outpatient department of Kathmandu Medical College Teaching Hospital, Sinamangal were followed up in the weekly asthma follow-up clinic on first of every week days. Children between the ages of 3-15 years on bronchodilator therapy for at least six months and attending the follow-up clinic from July 2001 to June 2002 were included in the study. Cases with pre-existing pulmonary disease, or systemic co-morbidity or those unable to cooperate in peak expiratory flow rate (PEFR) measurements were excluded from the study. Cases were categorized according to clinical features of asthma severity (as described by Global Initiative for Asthma, (GINA)²¹ as Intermittent, Mild persistent, Moderate persistent and Severe persistent groups (Table IA).

Children falling into severe persistent group were excluded from the study.

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Table 1A. Clinical features of asthma severity

Clinical Features of Asthma Severity	
Intermittent	Intermittent symptoms <1 time per week Brief exacerbations (from a few hours to a few days) Nighttime asthma symptoms <2 times a month Asymptomatic and normal lung function between exacerbations PEF or FEV ₁ : >80% of predicted; variability <20%
Mild persistent	Symptoms >1 time a week but <1 time per day Exacerbations may affect activity and sleep Nighttime asthma symptoms >2 times a month PEF or FEV ₁ : >80% of predicted; variability 20-30%
Moderate persistent	Symptoms daily Exacerbations affect activity and sleep Nighttime asthma symptoms >1 time per week Daily use of inhaled short-acting beta ₂ agonists PEF or FEV ₁ : >60% to <80% of predicted; variability >30%
Severe persistent	Continuous symptoms Frequent exacerbations Frequent nighttime asthma symptoms Physical activities limited by asthma symptoms PEF or FEV ₁ : <60% of predicted; variability >30%

Ketotifen (Privent-DT, Micro Labs) was given orally in the recommended therapeutic dose⁷⁻¹¹ (1mg twice daily) adjusted according to body weight²². (50 mcg/kg/dose) as far as practicable. It was continued over a period of 9 months and patients were evaluated at each follow up visit. Serial recording of frequency of asthmatic attacks, severity of exacerbations, PEFr measurements supplemented by detailed clinical examinations and enquiry from parents regarding patient quality of life were made.

Relevant investigations were done whenever appropriate and all known adverse effects^{7-11, 22} of Ketotifen were looked for, and recorded at each visit. Data was tabulated and analyzed to assess the efficacy and tolerability of Ketotifen in childhood asthma prophylaxis.

The primary outcome measures for judging the efficacy of Ketotifen comprised of decrease in frequency of asthmatic attacks and severity of exacerbations with improvements in peak expiratory flow rates (PEFR). Other measures

included decrease in bronchodilator requirement, steroid doses and parental perception regarding patient quality of life.

Results

Total number of patients enrolled in the study was 23 (i.e., 20M + 3F). MF Ratio = 6.66. The age distribution of patients is shown in Figure-1. Table -1 shows grouping of patients according to clinical features of asthma severity (as described by Global Initiative for Asthma (GINA)²¹ before commencing Ketotifen therapy. Maximum number of patients (13, 56.52%) belonged to Intermittent group while those in Mild persistent and Moderate persistent groups together constituted 43.47% of cases. The frequency of asthmatic attacks after beginning Ketotifen prophylaxis is shown in Table-2, while Table-3 presents the severity of exacerbations experienced during the treatment period. The serial recording of peak expiratory flow rate (PEFR) measurements during the same period is shown in Table-4.

Fig. 1 Age Distribution of patients

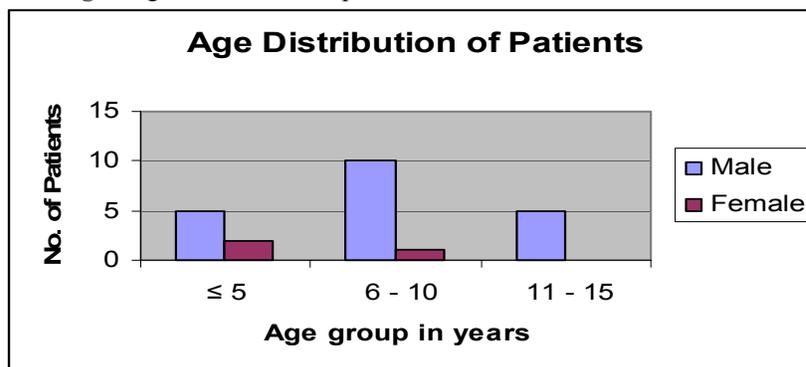


Table 1, Distribution of Patients according to clinical features of asthma severity (GINA, description in Table 1A)

Severity category	Age group in years			
	≤ 5	6 - 10	11 -15	≤ 5 - 15
Intermittent	4	6	3	13
Mild Persistent	3	4	2	9
Moderate Persistent	-	1	-	1
Severe Persistent	-	-	-	-

Table 2. Frequency of Asthmatic Attacks (After starting Ketotifen prophylaxis)

Age group in years	1 st 3 months				2 nd 3 months				3 rd 3 months			
	I	II	III	IV	I	II	III	IV	I	II	III	IV
≤ 5	4	3	-	-	2	2	-	3	1	-	-	6
6 - 10	6	4	1	-	4	3	-	4	3	1	-	7
11 -15	3	2	-	-	2	2	-	1	2	1	-	2

I = Symptoms < 1 time per week

II = Symptoms > 1 time a week but < 1 time per day

III = symptoms daily

IV = Symptomfree

Table 3. Severity of exacerbations (After starting Ketotifen prophylaxis)

Age group in years	1 st 3 months				2 nd 3 months				3 rd 3 months			
	I	II	III	IV	I	II	III	IV	I	II	III	IV
≤ 5	4	2	1	-	3	1	-	3	1	-	-	6
6 - 10	7	3	1	-	5	2	-	4	3	1	-	7
11 -15	3	2	-	-	2	2	-	1	2	1	-	2

I = Brief (from a few hours to a few days), do not affect activity and sleep

II = May affect activity and sleep

III = Affect activity and sleep

IV = Symptomfree

Table 4. Peak expiratory flow rate measurements (After starting Ketotifen prophylaxis)

Age group in years	1 st 3 months				2 nd 3 months				3 rd 3 months			
	I	II	III	IV	I	II	III	IV	I	II	III	IV
≤ 5	5	2	-	-	6	1	-	-	7	-	-	-
6 - 10	8	2	1	-	8	2	-	1	9	1	-	1
11 -15	3	2	-	-	2	2	-	1	4	1	-	-

I = PEFR > 80% of predicted, variability < 20%

II = PEFR > 80% of predicted, variability 20 - 30%

III = PEFR > 60% to <80% of predicted, variability > 30%

IV = 100% of predicted

Frequency of Asthmatic attacks

9 children (39.13%) had 'symptoms > 1 time a week but < 1 time per day' and one child (4.34%) had 'symptoms daily' at the beginning of the prophylactic Ketotifen therapy. At the end of 3rd 3 months only 2 (8.69%) had 'symptoms >1 time a week'. 8 children (34.78%) were symptom free by the end of 2nd 3 months and 15 children (65.21%) had no further attacks by the end of 3rd 3 months of Ketotifen prophylaxis. In ≤ 5 yr age group 6 of 7 children (85.71%) were symptom free whereas, 63.63% in 6-10 yr age group (7 of 11) and 40% in 11-15 yr age group (2 of 5) were also symptom free by the end of 3rd 3 months of Ketotifen prophylaxis.

Severity of exacerbations

Asthmatic exacerbations regularly 'affected activity and sleep' in 2 children (8.69%) and such tendency was present in 7 other children (30.43%) at the beginning of Ketotifen prophylaxis. At the end of 2nd 3 months of receiving Ketotifen 5 children (21.73%) remained 'likely to have disturbance of activity and sleep'. By the end of 3rd 3 months this figure reduced further to 2 children (8.69%) whose 'activity and sleep may be affected.' In the remaining 6 children (26.08%) who still experienced exacerbations the durations were found to be less than a few hours.

In the ≤ 5 yr age group 3 of 7 children (42.85%) had exacerbations 'which affect' or 'may affect activity and sleep'. In the 3rd 3 months after Ketotifen prophylaxis none of them had exacerbations of such 'severity'. Similarly, of 4 (36.36%) in the 6-10 year age group and 2 (40%) in 11-15 year age group children with such 'severity' of exacerbations were reduced to 1 in each of these age group (i.e., 9.09% and 20% respectively), following 3rd 3months of Ketotifen prophylaxis.

Peak Expiratory Flow Rate (PEFR) Measurements

6 children (26.08%) had PEFR>80% of predicted value with variability of 20-30% and one child (4.34%) had PEFR >60% to <80% of predicted value with variability >30% at the beginning of Ketotifen prophylaxis. By the end of 3rd 3 months only 2 children (8.69%) had PEFR>80% of predicted value with variability 20-30% and 20 children (86.95%) had variability <20% showing improvements.

Adverse effects of Ketotifen

Ketotifen was found to be remarkably well tolerated. No serious side effects were noted in any case throughout the trial period. Drowsiness was noted in 2 children (8.69%) aged 7 years and 11 yrs who complained of sleepiness in the classroom.

Discussion

This is a prospective, clinical trial using oral Ketotifen in children with asthma. We found significant decrease in symptom frequency and severity of exacerbation with improved parental perception regarding patient quality of life. Patient compliance was good without any dropouts among the participants indicating preference and adherence to oral therapy.

The result of this study is comparable to those reported by Baral et al²⁰ and therefore serves to support for a beneficial effect of oral Ketotifen in children with asthma. We found 8 out of 23 children (34.78%) symptomfree by 2nd 3 months, comparable to 9 out of 15 children (60%) free of symptoms after 6 months of therapy reported by Baral et al. This has to be viewed in the light of the difference that 30.43% of our patients were of age ≤5 years whereas Baral et al did not include ≤ 5 years children in their trial. In fact, these are the children who are unlikely to maximally benefit from inhaled asthma therapy and may need oral medication. In the remaining patients reduction in the use of bronchodilators and steroids was noted by us as was observed by Baral et

al. This steroid sparing effect of Ketotifen has long been documented⁸⁻¹¹. In our study PEFR measurements did not normalize rapidly although decrease in variability was evident. In other studies¹⁹ favorable effects of Ketotifen have been reported in Thai asthmatic children, although their raw data was not available for comparison.

A limitation of our study and several others is that we were unable to include an untreated, affected control group. But each patient acted his own control and only those children were given Ketotifen who were still symptomatic after at least 6 months on bronchodilator therapy (control group). We recognize that factors besides the oral Ketotifen therapy may contribute to the decreased frequency and severity rates in our patients. These factors include age-related understanding for avoiding allergens and triggering factors, genetic propensity, and changes in seasons during treatment period and in cases of some patients progression through or entrance into puberty. Asthma by itself is a heterogeneous condition in terms of course, severity and progression²³ and therapeutic options in this age group are not limited to drug management alone but avoidance of known

risk factors through effective parental education² also appears to be an important contributor. We did not observe any significant adverse effect of therapy during the study.

Whereas, inhalational therapy by the use of suboptimal delivery devices, by patient non-compliance and inability to cooperate may explain negative findings in some cases, oral Ketotifen must be considered as a beneficial prophylactic agent until better options become available for prevention of asthma, ideally for primary prevention²⁴.

Conclusion

Ketotifen is an orally active, well tolerated, safe prophylactic agent with beneficial effects in the preventive therapy of bronchial asthma. Our results indicate that oral Ketotifen therapy is effective and be considered for prophylaxis in children with asthma along with regular bronchodilator therapy.

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