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The Prophylactic Benefits of Twice-Daily Ketotifen in Asthmatic Saudi Children

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INTRODUCTION

Bronchial asthma is common in Riyadh, Saudi Arabia, particularly in children, yet despite the free availability of bronchodilator drugs, including metered-dose aerosols, there has been a great reluctance by parents and children to use medication consistently. The recent establishment of a pediatric asthma clinic at a major hospital in the city provided an opportunity for a group of patients to be seen on a regular basis by one physician. As part of this new program, different therapeutic modalities were examined, not only for their clinical effectiveness, but also for their social acceptability within the structure of the Saudi family and lifestyle.

Ketotifen offered a very simple, twice-daily tablet regimen that was both readily understood and accepted by patients. But reports of the effectiveness of ketotifen in bronchial asthma have been conflicting. A 16-week study was therefore initiated in which 39 children with bronchial asthma, frequent episodes of exercise-induced asthma (EIA), and objective evidence of airways obstruction were started on daily ketotifen and monitored by daily recording of symptoms and weekly clinic visits with measurements of peak expiratory flow rate (PEFR).

Despite the open nature of this study, controls being precluded by the limitation of primary care facilities outside the hospital, the clinical responses were so positive that they are detailed in this article.

Ketotifen was shown to be very effective as a regular prophylactic therapy in Saudi children, leading to substantial clinical improvements in asthma, with reduction in exercise-induced symptoms and increases in peak flow measurements exceeding 100% over 16 weeks.

METHODOLOGY

Patient Selection

Patients were selected for the study from those attending the routine pediatric asthma clinic at the Ministry of Health Maternity and Children's Hospital, Riyadh, Saudi Arabia. This older, well-established hospital

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serves the central area of the city, where the population is primarily Saudi.

Criteria for trial entry included a clear history of recurrent wheezing and coughing episodes together with frequent attacks of EIA, objective evidence of bronchial airways obstruction, a willingness by both patient and parents to participate in the study, and evidence of reliability in recording symptoms, taking medication, and attending follow-up clinics.

Details of patient characteristics at trial entry are summarized in Table 1.

Table 1. Description of Patients Who Completed the Study

Number and sex	32 Patients: 14 female, 18 male
Age	6-12 years (mean 8.6 years)
Race	28 Saudi, 4 Yemeni
Duration of asthma	1-6 years (mean 4.0 years)
Family history of asthma	17 Patients
Current therapy	Oral salbutamol: 21 patients Aminophylline: 10 patients No bronchodilators: 1 patient
PEFR (L/min)	80-180 (mean 120)
% Expected PEFR	38-89 (mean 63)

Study Design

The study was conducted over 16 weeks. After initial examination, all patients were started on ketotifen 1 mg twice daily throughout the trial. At entry all but one patient were using bronchodilators in some form, most commonly oral salbutamol twice daily. Drug use tended to be episodic. Patients were instructed to adhere to their previous regimen on a regular basis for the first 3 to 4 weeks of the trial, then to discontinue bronchodilator drugs unless clinical circumstances precluded this.

Patients were provided with a diary card on which they recorded the number of separate occasions each day or night that they experienced clear asthmatic symptoms with wheezing and/or coughing episodes. (Naturally, in their symptom recording, patients might differ in their interpretation of what constituted such episodes.) Data on attacks were entered daily, and a daily average calculated for each 4-week period.

The children exercised each day in an attempt to demonstrate their susceptibility to EIA. This often occurred with natural exercise but if it did not, the children, under parental guidance, ran for 5 minutes. EIA was recorded as 3+ if it occurred regularly with exercise, 2+ if only on some occasions, and 1+ if rarely. A cumulative score for each 4-week period was produced as the sum of the weekly average EIA scores.

Each week patients were assessed at the asthma clinic when their diary cards were examined and PEFR measured with a Wright peak flow meter (pediatric) recording the best of three separate readings. All patients were seen by the one physician (N.A.F.) at approximately the same time each week.

RESULTS

Thirty-nine patients entered the trial, and 32 successfully completed the full 16 weeks of observation. Seven patients failed to finish the study, because they either elected to withdraw or were excluded after unreliable recording or attendance. No patient was excluded for treatment failure.

Every patient showed a substantial clinical improvement over the 16 weeks. Data from each consecutive 4-week period were averaged. The recorded frequency of daily wheezing/coughing episodes, demands for emergency medical care, severity of EIA, and PEFR measurements are summarized in Table 2. The clinical indices of asthma severity declined by 50-70% over the observed period. This recovery was matched by a consistent rise in PEFR readings, which increased from a mean of 122 L/min (63% of predicted levels) during the first 4 weeks to 263 L/min (134% of predicted levels) in the final 4 weeks of the study. This represented an average increase in PEFR of more than 100% (range 55–158%). No patient exhibited a decline in clinical or measured feature of asthma severity.

Table 2. Clinical Assessment of Asthma During Study

INDEX		WEEK			
		1-4	5-8	9-12	13-16
Daily coughing episodes	Mean	4.2	3.0	1.7	1.3
	SD	3.0	2.1	1.1	0.8
EIA	Mean	8.9	5.1	4.1	3.5
	SD	0.3	0.2	0.2	0.2
Demands for emergency medical help	Mean	0.9	0.4	0.4	0.3
% Expected rise in PEFR	Mean	62	80	105	134
	SD	12.1	15.9	21.1	24.2

To compensate for the lack of a control group, the data were analyzed by calculating the individual changes in the various indices of asthma between different 4-week periods. Statistical evaluation of those paired differences is presented in Table 3, which shows, for daily coughing/wheezing, EIA, and PEFR, that there was a significant improvement between consecutive 4-week periods as well as overall. Significance of those changes in most instances revealed a probability of less than 0.0005.

The rise in PEFR was gradual through the first 12 weeks. Tables 2 and 3 reveal similar evidence of the progressive nature of the clnical improvement. Cessation of concomitant bronchodilator therapy after 3 to 4 weeks was not accompanied by any fall in PEFR or adverse trend in clinical features of the patients' asthma.

Despite the substantial clinical and PEFR improvement, almost all patients described some residual wheezing/coughing episodes at the trial's conclusion, but these averaged only 1.27 each day compared with 4.25 during the first 4 weeks of observation. Similarly, there were still demands for emergency medical treatment, although they were substantially reduced, averaging 0.3 calls per patient in the final 4 weeks (one call to each of 11 patients) compared with 0.9 calls (patients with up to five calls each) in the first 4 weeks.

Side effects of ketotifen therapy were reported by 14 of the 32 patients (43.7%), who complained of either drowsiness (seven patients) or dry mouth (seven patients). In general, these effects disappeared after the first 4 to 6 weeks of treatment, but on two instances dry mouth was

Table 3. Paired Changes in Clinical Indices of Asthma Between Different 4-Week Periods

INDEX		WEEKS COMPARED			
		5-8 vs. 1-4	9-12 vs. 5-8	13-16 vs. 9-12	13-16 vs. 1-4
Daily coughing episodes	Mean	− 1.3	− 1.3	− 0.4	− 3.0
	SEM	0.28	0.26	0.11	0.46
	p	0.0005	0.0005	0.001	0.0005
EIA	Mean	− 3.8	1.1	− 0.6	− 5.4
	SEM	0.28	0.24	0.22	0.37
	p	0.0005	0.0005	.005	0.0005
% Expected rise in PEFR	Mean	+17.8	+24.0	+28.0	+70.5
	SEM	1.77	2.15	2.37	3.16
	p	< 0.0005	< 0.0005	< 0.0005	< 0.0005

reported as a late, although minor problem. No patient required withdrawal of ketotifen because of unacceptable side effects.

Both physician and patients (or parents) assessed the overall clinical response to ketotifen as good in all patients.

DISCUSSION

The data reported above strongly suggest that ketotifen, in a twice daily regimen over 16 weeks, is an effective prophylactic drug for asthmatic children, giving both subjective and objective improvement. Almost all patients retained some residual symptoms, but these were mild in comparison with their entry recordings.

However, there are obvious difficulties with open uncontrolled trials such as this. It is impossible to determine how much improvement results from placebo effect (1) or how much from possible patient or physician bias, but improvement in PEFR averaged over 100% after 16 weeks despite the cessation of bronchodilator therapy after the first 3-4 weeks of the study, strongly implying a profound antiasthma effect from ketotifen. Placebo effects in asthma trials, whether the result of improved patient care, relaxation of patient anxieties, or adoption of regular bronchodilator therapy, tend to occur over the first 4-6 weeks of a study (Wilson JD, personal communication). In the present trial, clinical improvement continued for up to 16 weeks. Antiasthma effects of ketotifen are reported to develop slowly over 3 months, supporting the conclusion that some at least of the clinical improvement resulted from the drug (2,3).

PEFR levels at trial conclusion averaged 134% of expected values. The nomogram used for this calculation derived from the work of Godfrey et al. (4), who studied a group of English children. The 95% confidence limits are wide and encompass most results of the children in the Saudi Arabian study. Nevertheless, PEFR readings were consistently higher than those from English children of the same height.

Patients found ketotifen acceptable, with minimal side effects persisting beyond the first 2 to 3 weeks.

This open, preliminary study has shown, therefore, that ketotifen is a valuable treatment for children with bronchial asthma, reducing asthmatic symptoms, EIA, and therapeutic emergencies while substantially improving PEFR readings.

Szczeklik and his group (5) and Morris and Lane (6) have similarly found ketotifen to have clinical benefit in asthma. In contrast, a recent double-blind study with over 60 adult atopic asthmatics found no evidence for the efficacy of ketotifen (7).

The open nature of the study dictates that the conclusions are semiquantitative and preliminary only, but they do point the need for a formal double-blind trial of ketotifen in Saudi children.

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