A Clinical Trial of Ketotifen in Thai Asthmatics*

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SUMMARY **The efficacy of and tolerability to ketotifen, an oral prophylactic agent for bronchial asthma, were assessed in 39 Thai patients with chronic allergic asthma. A 1.0-mg dose was administered orally twice daily for four months. Asthmatic symptoms were significantly reduced as was the use of symptomatic medications. The drug's beneficial effects appeared from the end of the first month onward. Over-all assessment indicated highly therapeutic effects in 72 per cent of the patients treated; the use of ketotifen was ineffective in only 7.7 per cent of the cases.**

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Ketotifen, a benzocycloheptathiophene derivative, has recently been introduced for the prophylaxis of bronchial asthma. In addition to being an H_1-receptor antagonist, it has been shown to possess anti-anaphylactic properties which seem to be due to an inhibitory effect on the release of mediators from mast cells and basophils,[1] antagonism to the bronchoconstrictor effect of SRS-A,[2] and inhibition of cellular Ca^{++} uptake.[3] Results of a recent study suggest that it may also modify the beta-receptor function.[4]

The purpose of this study was to assess the prophylactic efficacy of this compound in treating a group of Thai asthmatics whose symptoms could not be effectively controlled with other medications.

MATERIAL AND METHODS

Thirty-nine patients (18 males and 21 females) with proven bronchial asthma, who had been receiving treatment at the Allergy Clinic of Pramongkutklou Hospital during the period from December 1980 to May 1982, were taken as subjects of this study. Their ages ranged from 13 to 51 years (mean:29.8 years). Twenty-nine of them had a definite family history of atopy.

All subjects had experienced asthmatic attacks for a period varying from 1 to 32 years (mean: 16.5 years) and had regularly been taking bronchodilators (sympathomimetics and /or theophyllines) and corticosteroids occasionally. Based on the severity of the disease prior to the institution of the trial, the patients were put into various categories: six of them were classified as mild cases (routine life not affected); 22, moderately severe cases (limited routine life owing to dyspnoea); and 11, severe cases (incapable of assuming a normal life-style).

The criteria for including patients in this study were: (1) FEV_1 and/or PEFR below 80 per cent of predicted values with more than a 15-per cent improvement effected by the administration of a bronchodilator and (2) positive intracutaneous reaction to two or more common allergens.

During the initial four weeks prior to the start of the drug trial, the patients were closely scrutinized for base-line conditions. For the ensuing 16 weeks, the patients took ketotifen (Zaditen®) starting with a dose of 0.5 mg orally twice daily during the first week; thereafter, 1 mg twice daily until the completion of the study. During the entire period of 20 weeks, symptomatic medications (bronchodilators, expectorants, antihistamines or corticosteroids) were to be used as necessary.

Patients were asked to record their symptoms (types, severity, frequency and duration of attacks) and the medications used in a diary provided for this purpose; they were also to come back for follow-up checks at one- or two-week intervals throughout the study period. During such follow-up visits, physical examinations, laboratory investigations (complete blood count, urinalysis and liver function test) and pulmonary function studies

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(FEV_1 and/or PEFR) were conducted.

An assessment of the efficacy of ketotifen and the patients' tolerability to it was made, using monthly summaries from the patients' diary in which were recorded their asthmatic symptoms and use of symptomatic medications; also used were the results of the regular physical examinations, pulmonary function studies, and laboratory investigations as well as the patients's complaints concerning any adverse effects. Scores were calculated on the following basis: *symptom scores*- cough, 1 point; chest oppression, 2 points; and breathlessness, 4 points (the severity, frequency and duration of attacks were all scored on the basis of these symptoms); *medication scores*- use of oral or inhalant bronchodilators, 1 point per dose; antihistamines or expectorants, 1 point per dose; and corticosteroids, 4 points per dose.

At the conclusion of the study, the efficacy of ketotifen was classified into four categories: *very effective*, for asymptomatic cases requiring no symptomatic medication; *effective*, cases with a 50-per-cent or more improvement in asthmatic symptoms and/or reduction of attacks and/or decreased use of symptomatic medications; *slightly effective*, cases with some improvement in symptoms and a reduction in the number of attacks to less than 50 per cent, although their consumption of symptomatic medications remained unchanged; and *ineffective*, cases with no improvement at all.

RESULTS

With the institution of ketotifen therapy, there was a trend towards an improvement in asthmatic symptoms based on the scores calculated from patients' diaries; this trend was noted from the end of the first month ($p < 0.05$); the severity and frequency of symptoms were reduced by the end of the third month ($p < 0.05$).

Based on the interviews and physical examinations during each visit, it was noted that at the end of the first month 14 patients (36 per cent of the total number of cases) were exhibiting asthmatic symptoms and signs. The number was reduced to 10 patients (25.6 per cent of the total) at the end of the second month. Nine patients (23 per cent of the total) were entirely free of symptoms and signs at the end of the study. Only 3 patients (7.7 per cent of the total) did not show any improvement from the beginning of the study to the end. A bar histogram (Fig. 1) shows the number of patients with symptoms and signs at the end of each month of observation.

With regard to the use of symptomatic medications, ketotifen showed its beneficial effects from the first month to the end of the study period as evidenced by the reduction in the medication scores (Fig. 2). A reduction in the mean monthly scores regarding the use of sympathomimetics, although apparent, was not

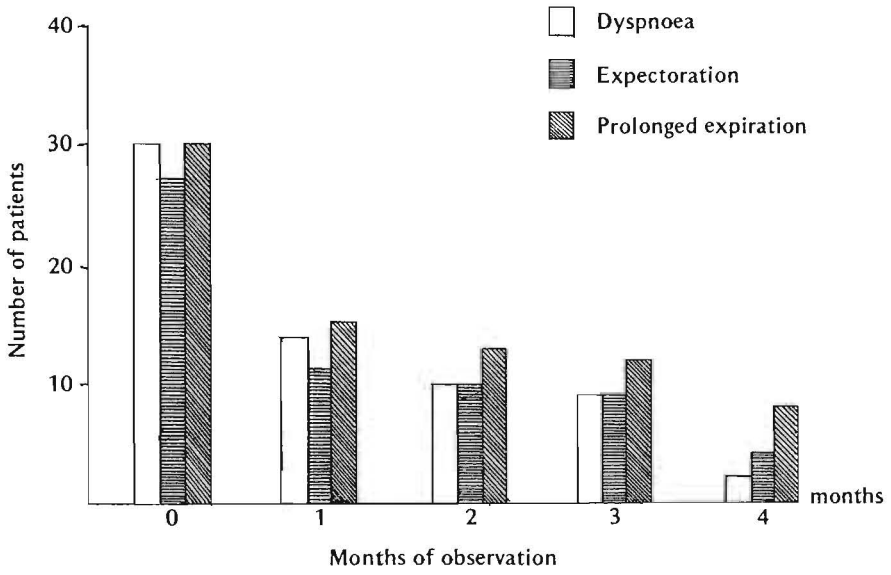

Fig. 1 Histogram showing number of patients with symptoms and signs at the end of each month.

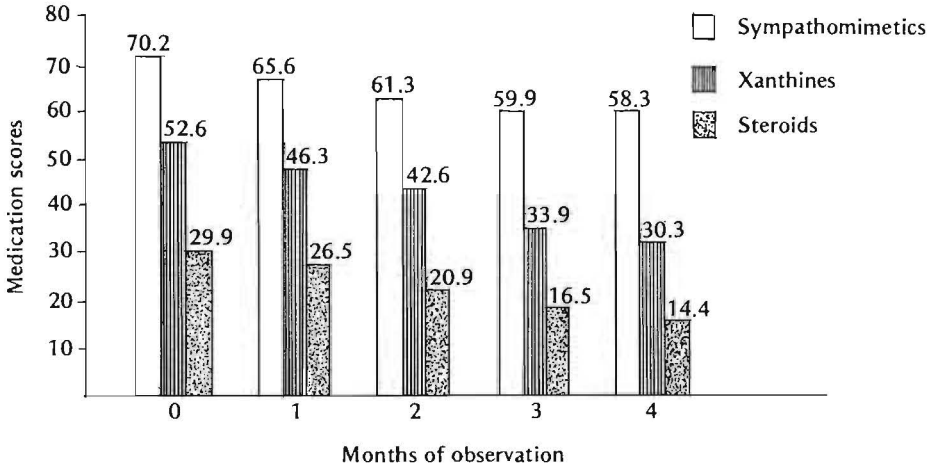

Fig. 2 Reduction in symptomatic medications

statistically significant ($p > 0.05$). However, two patients were able to discontinue the use of these drugs at the end of their fourth week on ketotifen; five were able to do likewise at the end of the study.

The reduction in xanthine usage from the first month was of statistical significance ($p < 0.05$). At the end of the fourth week, 10 patients (29.4 per cent of the 34 cases who took theophyllines) were able to discontinue the use of the drug; at the end of the trial, 15 patients (44.1 per cent of the 34 cases) were able to completely stop using xanthines. In the latter group, 10 were males, and all were between 17 and 42 years of age. By the end of the second month, there was also a considerable reduction in the mean monthly scores for corticosteroid usage ($p < 0.05$). At the end of the fourth week, 4 patients (15.3 per cent of the 26 cases who took corticosteroids) were able to discontinue such medication, and at the end of the trial 12 patients (46.1 per cent of the 26 cases) were able to discontinue use of such drugs completely.

Pulmonary function data obtained prior to and during the trial showed a trend towards improvement but the trend was not statistically significant.

Figure 3 shows the four-category classification made at the end of the trial. Seven patients (19.7 per cent of the total) responded excellently to ketotifen; 21 patients (53.8 per cent of the total) did fairly well; and eight (20.5 per cent of the total) improved to some degree. Three patients (7.7 per cent of the total) did not respond to the prophylactic treatment with ketotifen. The non-responders were a 13-year-old boy and 2 women aged 31 and 36 years, respectively; all were steroid dependent.

Throughout the study, all laboratory findings were within normal limits.

There were 17 patients (43.5 per cent of the total) who reported drowsiness and dryness of the mouth during the first few days of ketotifen therapy, but the symptoms were mild and transient and did not interfere with the patients' daily activities.

DISCUSSION

The over-all results of this trial have shown that the prophylactic use of ketotifen was efficacious in about 72 per cent of the asthmatics involved in the study. The findings conformed closely to the experience of other investigators.[1,5,10]

According to the data recorded in this study, the beneficial effects of ketotifen became apparent towards the end of the fourth week of treatment; therefore, it would be advisable that an appropriate bronchodilator always be used concurrently with ketotifen during the initial period of one to two months, and thereafter be gradually withdrawn according to the patient's response.

The convenience of taking this oral drug twice a day made it well accepted by all the patients. Such compliance is certainly needed for the long-term management of any chronic illness such as bronchial asthma. At this point it is possible to advocate the use of ketotifen as another anti-asthmatic drug for the effective prophylaxis of acute asthmatic attacks. The drug is safe and well-tolerated by most patients.

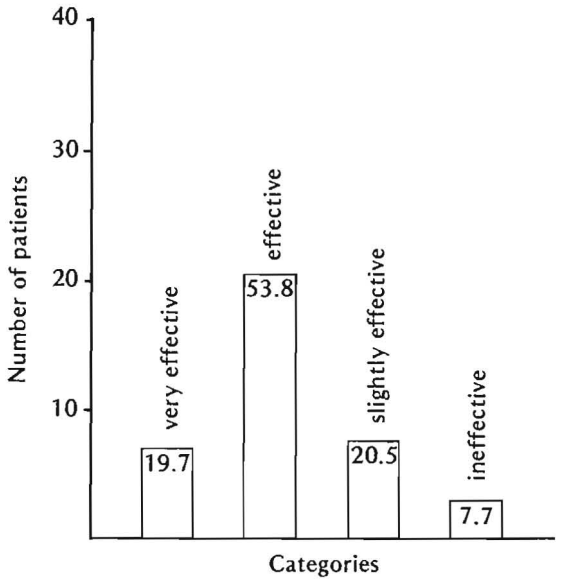

Fig. 3 Results of treatment

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