plasma glucose concentrations of 4 to 7 mmol/l (72-126 mg/100 ml) were not achieved in all patients, because some left hospital before complete adjustment of their insulin dose had been made. Several patients still had unsatisfactory noon plasma glucose concentrations, indicating the need for additional "quick-acting" insulin in the morning.

In our study 21% of the patients suffered an episode of presumptive nocturnal hypoglycaemia, whereas Gale and Tattersall reported an incidence of 56%[2]; the comparable mean reductions in insulin dose required for good diabetic control were 23% and 25%. There is little information on the overall incidence of nocturnal hypoglycaemia in insulin-requiring diabetes, and both we and Gale and Tattersall[2] in some way selected the subjects for study.

Our results strongly support the view that measuring the cortisol to creatinine ratio in an overnight urine specimen is a useful detector of an otherwise unrecognised nocturnal hypoglycaemic event. The test is straightforward and may be performed on a specimen collected by any co-operative continent patient, including outpatients. It provides a simple means of detecting poor glucose regulation caused by overtreatment with insulin and yields clear separation of normal and abnormal results. As well as serving as a guide to insulin treatment, it may elucidate how overtreatment with insulin causes unstable diabetes.

Several causes of false-positive results, however, will probably be recognised with continued study; Cushing's syndrome would be one cause, as would severe depression and a major physical upset such as nocturnal pulmonary embolism.

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Ketotifen in adult asthma

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Summary and conclusions

The efficacy and adverse effects of ketotifen 1 mg twice daily and 2 mg twice daily were compared with placebo in 50 patients with atopic asthma in a multicentre, double-blind study. Ketotifen in the higher dosage caused a slight reduction in salbutamol usage and a modest improvement in breathing in patients not already receiving inhaled corticosteroids. The drug was ineffective in patients receiving inhaled corticosteroids. Drowsiness was a troublesome effect causing withdrawal from treatment or reduction of dosage in seven patients while receiving ketotifen compared with only three while receiving placebo.

This study was designed by Dr A J Dyson on behalf of a subcommittee of the Research Committee of the British Thoracic Association, whose members were: Drs Elizabeth A Hills (chairman), A J Dyson, J A R Friend, R Greenwood, A D Mackay, C Skinner, and P Smith. The study was co-ordinated and the report prepared by Dr A D Mackay, whose research fellowship was also supported by the Chest, Heart and Stroke Association.

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Thus the slight beneficial effect of ketotifen on asthma must be balanced against its side effect of drowsiness.

Introduction

Sodium cromoglycate benefits asthmatic patients.[1] Oral antiallergic compounds that like cromoglycate inhibit anaphylactic mediator release in laboratory models have now been synthesised. These might benefit patients unable to use an inhaler efficiently. One of these compounds, ketotifen, is a benzocycloheptathiophene derivative that shows potent antianaphylactic and antihistaminic activity in animals. Ketotifen also inhibits chemically induced release of histamine from rat peritoneal mast cells by compound 48/80 in vitro.[2] Oral ketotifen has shown a protective effect against allergen-induced bronchoconstriction in adults with atopic asthma[3] but not in children.[4] We report a longer-term comparison of ketotifen and placebo in adult asthma.

Patients and methods

We recruited 50 patients (34 men and 16 women) aged 16-66 years (mean age 36 years) from 12 centres. All had a forced expiratory volume in one second (FEV_1) above 40% of their predicted value, reacted to skin-prick tests with common allergens, and showed a greater than 20% improvement in FEV_1 after inhaling a bronchodilator. Patients taking tablets of corticosteroid were excluded, but those who inhaled a constant dosage of corticosteroid were included. Patients in whom the potential effect of drowsiness might have proved dangerous were not eligible. Sodium cromoglycate was not permitted during the four weeks before entry. Bronchodilators other than inhaled salbutamol for symptomatic relief were stopped.

The trial was conducted double-blind, and patients received each of the following regimens for one month in random order: (1) ketotifen 1 mg twice daily, (2) ketotifen 2 mg twice daily, and (3) placebo capsules twice daily. Patients were told to use their salbutamol inhaler only to relieve symptoms, and to record the number of puffs taken and their timing on daily diary cards. Two measurements of peak expiratory flow rate (PEFR) were made three times daily and recorded on the diary card. Patients were asked to measure PEFR before inhaling salbutamol if possible, as readings made within four hours after salbutamol would not be used when calculating the mean PEFR. On the diary cards the patients also recorded self-assessments on line diagrams of daytime and nocturnal dyspnoea, rhinorrhoea, pricking eyes, and itching of the skin. The line diagrams were 50 mm long and were marked by the patients to express quantitatively their impressions of each particular symptom. A weekly score (mm) for the subjective impression of each symptom was calculated by adding daily scores. Patients attended every two weeks and were questioned about side effects. At each visit the used diary cards were collected and drugs and diary cards for the subsequent period issued.

One capsule was taken from each of two numbered containers night and morning. If a patient reported intolerable drowsiness when reviewed after two weeks, capsules from container 2 were stopped; this halved the regimen consisting of 2 mg twice daily but left the other two regimens unchanged for the remainder of that treatment period. Any patient continuing to be drowsy despite this manoeuvre was withdrawn. Blood tests were taken at entry and at the end of each treatment period. Patients who suffered an exacerbation of asthma requiring oral corticosteroids were withdrawn and regarded as treatment failures.

Results

Four patients withdrew from the trial because of drowsiness: one while receiving placebo, two while receiving the lower-dosage ketotifen regimen, and one while receiving the higher-dosage regimen. One patient who continued sodium cromoglycate treatment was excluded. Three patients who experienced exacerbations of asthma withdrew as treatment failures.

Five of the remaining 42 patients halved their daily number of study capsules during the trial because of drowsiness. This occurred with only the placebo regimen (one patient), with the placebo and higher-dosage ketotifen regimens (one), with both ketotifen regimens(one), and with only the higher ketotifen dosage (two). Four patients thus changed from the higher to the lower ketotifen dosage because of drowsiness, and their results were excluded from further analysis. Thirty-eight patients therefore remained for analysis, 15 of whom were maintained on inhaled steroids. To reduce the possibility of a carry-over effect from one treatment period to another, analysis was based on the results for the last two weeks of each treatment period. Patients were compared according to whether they used salbutamol alone or inhaled salbutamol plus corticosteroids as additional treatment.

For the appropriate weeks mean PEFR was calculated after excluding readings taken within four hours after salbutamol inhalation. There was no significant difference in PEFR for any treatment period in either group of patients (table). Ketotifen 2 mg twice daily reduced salbutamol usage by a mean of 5 puffs/week and improved daytime breathlessness only in those patients not already receiving inhaled corticosteroids ($p < 0.05$ for both variables). A beneficial effect on itching was also seen in the same group of patients at this higher ketotifen dosage ($p < 0.02$). Scores for nasal and eye symptoms showed no significant difference for any treatment period.

No haematological or biochemical changes occurred during any treatment period.

Mean results obtained during last two weeks of treatment with placebo and ketotifen 1 mg and 2 mg twice daily in patients taking inhaled salbutamol or inhaled corticosteroids and salbutamol as additional treatment

	Inhaled salbutamol (n = 23)			Inhaled corticosteroids and salbutamol (n = 15)		
	Placebo	Ketotifen		Placebo	Ketotifen	
		1 mg	2 mg		1 mg	2 mg
PEFR (l/min)	337	330	335	313	314	309
Salbutamol usage (puffs/week)	24	22	19*	29	26	26
Symptom scores†:						
Breathing:						
Day	241	247	266*	285	288	270
Night	250	264	285	286	294	260
Itching of skin	314	326	325**	328	318	328

PEFR = Peak expiratory flow rate.
Significance of difference when compared with placebo: *P < 0·05, **P < 0·02 (Wilcoxon rank sum test for paired differences).
†Maximum possible score one week on line diagrams = 350; a higher score compared with that for placebo represents improvement.

Discussion

Ketotifen in a dosage of 2 mg twice daily reduced salbutamol usage and improved symptom scores for breathing only in the patients who were not already receiving inhaled corticosteroids. The differences, however, were small, and at this dosage more patients experienced drowsiness. In addition, three patients withdrew as treatment failures because of exacerbations of asthma requiring oral corticosteroids while they were receiving active treatment. The patients maintained on inhaled steroids recorded higher symptom scores for breathing while receiving placebo than those taking only additional salbutamol, and they may therefore have had less potential for improvement.

PEFR showed no improvement with ketotifen, but in previous studies of sodium cromoglycate in adult asthma benefit has usually been shown by patient preference[5] or a reduction in other treatment[6] rather than by improvement in pulmonary function. Therefore, we assessed the response to each dosage of ketotifen and to placebo in several ways—namely, by withdrawal from the study, thrice-daily readings of PEFR, daily usage of a bronchodilator inhaler, and subjective assessments of symptoms —to avoid underestimating the value of the drug.

Ketotifen has shown superiority over the antihistamine clemastine in treating atopic asthma[7] and has provided protection against acute antigen challenge[3] and histamine challenge.[8] In the present placebo-controlled study, however, ketotifen's beneficial effect on asthma appears slight and must be balanced against the effect of drowsiness, which was severe enough to cause seven patients (14%) to withdraw from treatment or reduce the dosage.

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