Does regular treatment with ketotifen inhibit bronchoconstriction induced by isocapnic hyperventilation?

P. RAFFERTY, P. M. TWEEDDALE, R. J. FERGUSON, B. A. BIGGS & I. W. B. GRANT

Northern General Hospital, Ferry Road, Edinburgh and Department of Respiratory Diseases, University of Edinburgh, Edinburgh

Eight asthmatic patients completed a 12-week, double-blind, placebo controlled study to assess the efficacy of ketotifen, 1 mg twice daily, in the inhibition of bronchoconstriction induced by isocapnic hyperventilation (IH). There was no significant difference in the degree of bronchoconstriction produced by IH after treatment with ketotifen or placebo.

Keywords ketotifen isocapnic hyperventilation bronchoconstriction

Introduction

Ketotifen is a benzocycloheptathiophene derivative which is a potent antihistamine *in vivo* (Craps *et al.*, 1978; Esau *et al.*, 1984) and has been shown to act as a mast cell stabilizer *in vitro* (Martin & Romer, 1977). Several studies have demonstrated inhibition by ketotifen of histamine-induced (Craps *et al.*, 1978) and allergen-induced (Craps *et al.*, 1978; Palmen, 1983) bronchoconstriction, but reports of its efficacy in exercise-induced asthma (EIA) are conflicting (Craps *et al.*, 1978; Dorward & Patel, 1982; Petheram *et al.*, 1981; Kennedy *et al.*, 1980; Lilja *et al.*, 1983). Most of these studies were performed after 3 weeks or less of treatment with ketotifen and it has been suggested that the maximum effect may not be achieved until 5 weeks after treatment has been commenced (Gobel, 1978).

Isocapnic hyperventilation (IH) is thought to produce its effects on asthmatic airways in a manner analogous to that of exercise, namely cooling and drying of the airways (Zeballos *et al.*, 1978; McFadden & Ingram, 1979). We now report on a 12 week, double-blind, placebo-controlled crossover study performed to assess the efficacy of ketotifen, 1 mg twice daily, in inhibiting bronchoconstriction induced by IH.

Methods

Twelve mild asthmatics (five males, seven fe-

males, mean age 28.6 ± 9.3 years) entered the study with their informed consent. They had a mean forced expiratory volume in one second (FEV_1) on entry of 3.15 ± 0.97 l min⁻¹ (mean $\pm$ s.d.). All gave a history of EIA and had previously been shown to develop significant bronchoconstriction (greater than a 15% fall in FEV_1) following 6 min of IH. Their asthma was controlled using inhaled β_2 -adrenoceptor agonists with or without inhaled corticosteroids. Those patients on treatment with sodium cromoglycate or theophylline preparations were excluded from the study.

At the start of the study IH was performed as previously described (Tweeddale *et al.*, 1981). The target hyperventilation rate for each individual was set as the 4 min maximum voluntary ventilation (predicted from FEV_1 by the formula of Clark *et al.*, 1969). The method was modified to cool the dry inspired air to 6–10° C by passing the gas through a heat exchanger containing ice. Measurements of FEV_1 were made before IH and at 1, 5, 10 and 15 min thereafter. On each occasion the highest value of three technically acceptable manoeuvres was recorded. This procedure was repeated at the same time of day 6 and 12 weeks later.

During the first 6 week period patients were allocated to receive either ketotifen (1 mg) or placebo capsules, one twice daily, and during the

second 6 week period they were changed to the alternative treatment. Since drowsiness can initially be a problem with ketotifen the active treatment comprised a placebo tablet in the morning and 1 mg of ketotifen at night for the first 2 weeks, and 1 mg of ketotifen twice daily for the remaining 4 weeks. Patients were asked to withhold all medication for 12 h prior to each IH study.

Data analysis

Analysis of variance was used to assess any differences between the baseline FEV₁ values obtained on the three study days. Following IH, the maximum fall in FEV₁ was expressed as a percentage of the starting baseline value and comparisons between the three study days were again made by analysis of variance.

Results

Of the twelve patients who entered the study, two were withdrawn, one in the first week because of cold extremities (subsequently found to be on placebo) and one for failure to comply with the treatment protocol. Two further patients defaulted. There were no significant differences in the baseline FEV₁ values on each of the three study days. Isocapnic hyperventilation performed on entry to the study, after 6 weeks treatment with ketotifen and after 6 weeks on placebo produced significant bronchoconstriction in all but one patient, with falls in FEV₁ of greater than 15% from baseline value (Table 1). There was no significant difference between the response to isocapnic hyperventilation carried out before the start of the trial, after 6 weeks on ketotifen or after 6 weeks on placebo, with falls in FEV₁ of 43.9 ± 6 , 37.5 ± 6 and $47.9 \pm 6\%$

(mean $\pm$ s.e. mean) respectively. When direct comparison was made between the response after ketotifen and that after placebo the mean difference between these falls was 10.45 with wide 95% confidence limits of -3.75 to 26.62 . The study had a 75% chance of detecting a 20% difference between the bronchoconstrictor responses to IH following placebo or ketotifen and a 95% chance of detecting a 50% difference in the responses.

One patient (number 4) whose FEV₁ fell by over 60% following IH both on entry to the study and after 6 weeks on placebo, appeared to benefit from ketotifen with a fall of only 11% in FEV₁ following IH after 6 weeks of the active treatment. Of the eight patients who completed the study only one noticed drowsiness during treatment with ketotifen. No other side effects were reported.

Discussion

Isocapnic hyperventilation and exercise have been shown to produce closely correlated degrees of bronchoconstriction (Tweeddale *et al.*, 1981; Deal *et al.*, 1979). Craps *et al.* (1978) reported inhibition of EIA following 4 days of treatment with ketotifen but this effect could not be confirmed by others following ketotifen given in single dose (Dorward & Patel, 1982), for 4 days (Kennedy *et al.*, 1980), for 1 week (Lilja *et al.*, 1983) or for 4 weeks (Petheram *et al.*, 1981). These results might be attributed to inadequate duration of treatment with ketotifen since it has been reported that ketotifen may achieve maximal efficacy only after 5 weeks of treatment (Gobel, 1978). Comparable studies have not so far been reported on the protective effect of ketotifen against bronchoconstriction induced by isocapnic hyperventilation. The present study is an attempt

Table 1 The maximum falls in FEV₁ following isocapnic hyperventilation (expressed as a percentage of the baseline FEV₁)

Patient	On entry	At the end of 6 weeks	
		Ketotifen	Placebo
1	16.3	16.5	15.9
4	62.7	11.2	68.6
5	60	57.8	45
7	37	29.6	39.6
9	48.9	48.3	41.8
10	52	53	54.3
11	52	40.8	67.3
12	23	42.4	50.7
Mean $\pm$ s.e. mean	43.9 ± 6	37.5 ± 6	47.9 ± 6

to fill that gap, taking into account the claim made by Gobel (1978). In this study it has been shown that despite treatment with ketotifen for 6 weeks, there was no significant inhibition of the bronchoconstriction induced by IH, although in one patient the response to IH was attenuated by ketotifen. These results are in keeping with the findings of others (Lilja *et al.*, 1983) who reported no overall beneficial effect of ketotifen against exercise-induced asthma, but describe individuals showing marked benefit. Our results suggest

that, in general, even prolonged treatment with ketotifen does not moderate the bronchoconstrictor response to IH. Although there are *a priori* grounds for extrapolating this result to exercise-induced asthma, there are those who believe that the two forms of challenge may operate via different mechanisms (Godfrey, 1986) and therefore only a study based directly on exercise-challenge will resolve what remains a controversial issue.

References

- Clark, T. J. H., Freedman, S., Campbell, E. J. M. & Winn, R. R. (1969). The ventilating capacity of patients with chronic airways obstruction. *Clin. Sci.*, **36**, 307–316.
- Craps, L., Greenwood, C. & Radielovic, P. (1978). Clinical investigation of agents with prophylactic anti-allergic effects in bronchial asthma. *Clin. Allergy*, **8**, 373–382.
- Deal, E. C., McFadden, E. R., Ingram, R. H. & Jaeger, J. J. (1979). Hyperpnoea and heat flux: Initial reaction to exercise-induced asthma. *J. appl. Physiol.*, **46**, 476–483.
- Dorward, A. J. & Patel, K. R. (1982). A comparison of ketotifen with clemastine, ipratropium bromide and sodium cromoglycate in exercise-induced asthma. *Clin. Allergy*, **12**, 355–361.
- Esau, A. del Carpio, J. & Martin, J. G. (1984). A comparison of the effects of ketotifen and clemastine on cutaneous and airway reactivity to histamine and allergen in atopic subjects. *J. Allergy clin. Immunol.*, **74**, 270–274.
- Gobel, P. (1978). The protective effect of ketotifen in bronchial asthma. *J. int. med. Res.*, **6**, 79–85.
- Godfrey, S. (1986). Controversies in the pathogenesis of exercise induced asthma. *Eur. J. resp. Dis.*, **68**, 81–88.
- Kennedy, J. D., Hashan, F., Clay, M. J. D. & Jones, R. S. (1980). Comparison of the action of disodium cromoglycate and ketotifen on exercise-induced bronchoconstriction in childhood asthma. *Br. med. J.*, **2**, 1458.
- Lilja, G., Graff-Lonnevig, V. & Bevegard, S. (1983). Comparison of the protective effect of ketotifen and disodium cromoglycate on exercise-induced asthma in asthmatic boys. *Allergy*, **38**, 31–35.
- Martin, U. & Romer, E. (1977). Ketotifen: a histamine release inhibitor. *Monographs in allergy*, **12**, 145–149.
- McFadden, E. R. & Ingram, R. H. (1979). EIA: new observations on the initiating stimulus. *New Engl. J. Med.*, **301**, 763–769.
- Palmen, F. M. L. H. G. (1983). Antigen bronchial challenge and efficacy after four weeks of treatment with ketotifen and disodium cromoglycate. *Respiration*, **44**, 103–108.
- Petheram, I. S., Moxham, J., Bierman, C. W., McAllen, M. & Spiro, S. (1981). Ketotifen in atopic asthma and exercise induced asthma. *Thorax*, **36**, 308–312.
- Tweeddale, P. M., Godden, D. J. & Grant, I. W. B. (1981). Hyperventilation or exercise to induce asthma? *Thorax*, **36**, 596–598.
- Zeballos, R. J., Shturman-Ellstein, R., McNally, J. F., Hirsch, J. E. & Souhdra, J. F. (1978). Role of hyperventilation in exercise-induced bronchoconstriction. *Am. Rev. resp. Dis.*, **118**, 877–884.

(Received 20 November 1986,
accepted 27 February 1987)