EFFECTS OF ORAL H₁ AND H₂ RECEPTOR ANTAGONISTS IN ASTHMA

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- 1 There is evidence that H₂ receptors are present in the lung, both on bronchial smooth muscle and mast cells. In animal studies, stimulation of H₂ receptors causes a diminution, and conversely H₂ receptor blockade can increase, smooth muscle contraction and mediator release.
- 2 The effects of H₂ receptor blockade in ten patients with asthma has been studied using oral cimetidine in a dose of 1g daily for 1 week. Treatment was compared with placebo and the H₁ receptor antagonist chlorpheniramine.
- 3 There was no alteration in the severity of naturally-occurring or exercise-induced asthma with cimetidine or chlorpheniramine.
- 4 H₂ receptor blockade with oral cimetidine in conventional doses is without ill effect in asthma. The use of larger parenteral doses is discussed.

Introduction

Although the role of histamine in the pathogenesis of asthma remains uncertain, the association of histamine release and tissue anaphylaxis with bronchoconstriction is well established. The observations that allergen-induced human bronchial muscle contraction *in vitro* is partially antagonised by the H₁ receptor antagonist mepyramine maleate (Dunlop & Smith, 1977), and that intravenous chlorpheniramine maleate (Popa, 1977) and inhaled clemastine fumarate (Nogrady, Hartley, Handslip & Hurst, 1978) cause bronchodilatation in asthmatic subjects, suggests that histamine does directly participate in asthmatic bronchospasm.

Conversely, H₂ receptor antagonists potentiate allergen-induced bronchoconstriction, both in human bronchial muscle (Dunlop & Smith, 1977) and in sensitized guinea-pigs (Drazen, Venugopalan & Soter, 1978). H₂ receptor blockade by cimetidine, used for the management of peptic ulceration, might therefore cause deterioration in respiratory function in asthmatic patients. The studies described in this paper were performed to investigate this possibility.

Methods

Ten stable asthmatics aged 17–54 years (mean 34.8), eight of whom were regarded as atopic on the basis of history and positive skin tests, and eight of whom had exercise-induced asthma, agreed to participate in a clinical trial lasting four weeks, comparing by a

double-blind, double-dummy technique, the effects of oral cimetidine with the H₁ antagonist chlorpheniramine, and placebo. During the first and third weeks of the trial placebo medication only was taken, during the second and fourth weeks either cimetidine 200 mg three times daily and 400 mg at night or chlorpheniramine 4 mg three times daily and placebo at night was randomly prescribed; the dose of oral (one patient) and inhaled corticosteroids (three patients) and disodium cromoglycate (one patient) were not changed during the trial. The response was assessed by means of a diary card, recording symptoms, bronchodilator usage and twice daily peak flow rates (PFR) using a Peak Flow Gauge (Airmed), and at the end of each week a standardized exercise provocation test was performed on a cycle ergometer (Miller, Davies, Cole & Seaton, 1975). Bronchodilators and disodium cromoglycate were omitted for 12 h, and the last dose of trial drug taken 2 h before each exercise test. At the end of the trial the diary card data were reduced to the mean values for each week. The ratios of the lowest post-exercise FEV₁ and PFR (best of three attempts) to the pre-exercise values for all patients were calculated and the results for each treatment period were compared by Student's *t*-test.

Results

The results are summarized in Table 1. Neither the group as a whole nor any individual patient showed

significant changes in symptom scores, bronchodilator usage or daily peak flow rates during treatment with cimetidine, chlorpheniramine or placebo. There was no significant difference in the degree of exercise induced asthma between active and placebo treatment weeks.

Discussion

The need for high local tissue concentrations of antihistamines to prevent allergen-induced bronchospasm *in vitro* was shown many years ago (Schild, Hawkins, Mongar & Herxheimer, 1951), although bronchial muscle contraction caused by exogenous histamine could be inhibited by much lower doses. It is not surprising therefore that H_1 receptor antagonists when given orally in conventional doses are ineffective in controlling asthmatic symptoms, although their failure to do so has been a major factor leading to the concept of histamine as an important mediator of asthmatic bronchospasm falling into disrepute.

The recent observations that higher tissue levels of H_1 receptor antagonists achieved by parenteral administration (Popa, 1977) or by inhalation (Nogrady *et al.*, 1978) can cause bronchodilatation suggests that histamine does perhaps contribute to the development of bronchospasm in asthma. Further indirect evidence for this has been obtained by Simon, Stevenson, Arroyave & Tan, (1977), who found a correlation between plasma histamine levels and the severity of airways obstruction in asthmatic patients.

Normal human bronchus *in vitro* contracts in response to histamine, but when H_1 receptor blockade is complete, histamine is a weak bronchodilator (Dunlop & Smith, 1977). This effect is mediated by an H_2 receptor, since it is abolished by metiamide. It would appear therefore that both H_1 and H_2 receptors exist in the human bronchus, the effect of

the latter being to reduce the bronchoconstrictor effects of the former. Receptors of the H_2 type may also be present on mast cells, since the addition of histamine to rat peritoneal mast cell preparations can inhibit release of mediator substances, and this effect can be blocked by an H_2 receptor antagonist (Lichtenstein, 1975).

Blockade of H_2 receptors in asthma would, therefore, on the basis of these studies, result in unopposed H_1 muscle receptor activation, and augmented mediator release from tissue mast cells which would exacerbate asthmatic bronchospasm. Evidence exists that this occurs in allergic human bronchospasm (Dunlop & Smith, 1977) and in allergic bronchospasm in guinea pigs (Drazen *et al.*, 1978).

The results of this study show that the oral administration of the H_2 receptor antagonist cimetidine does not influence the clinical state of asthmatic patients, or cause increased bronchoconstriction following exercise challenge.

Drazen *et al.*, (1978) have suggested that the pharmacology of cimetidine may differ from the earlier H_2 receptor antagonists burimamide and metiamide as they were unable to produce increased bronchoconstriction following challenge in sensitized guinea pigs using this H_2 receptor blocking drug, whereas both the other drugs were effective. This remains to be clarified. However, the lack of effect of oral cimetidine in our subjects may well have been for the same reason that oral H_1 receptor blocking drugs are ineffective in asthma, namely that tissue levels in the bronchi are lower. For this reason, we suggest that the use of large parenteral doses of cimetidine should be considered with caution in asthma, until more is known of the pharmacology of the drug, and the role of H_2 receptors in the human bronchus.

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Table 1 Effect of H_1 and H_2 receptor antagonists on daily PFR and exercise-induced asthma

	Number of patients	Placebo (week 3)	Cimetidine (week 2 or 4)	Chlorpheniramine (week 2 or 4)
Mean morning PFR (litre/min)	10	422 ± 148	420 ± 141	423 ± 157
Mean evening PFR (litre/min)	10	449 ± 135	447 ± 111	475 ± 122
% fall in PFR after exercise	8	22.1 ± 14.7	25.0 ± 8.8	23.5 ± 8.1
% fall in FEV ₁ after exercise	8	18.9 ± 11.4	22.4 ± 11.6	21.3 ± 12.8

Results are mean values ± s.d. $P > 0.1$ for all intergroup comparisons (paired *t*-test).

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