

H2 receptor blockade and bronchial hyperreactivity to histamine in asthma

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ABSTRACT The role of histamine H1 and H2 receptors in the lung is not clear. H1 receptor blockade results in bronchodilatation and inhibition of histamine induced bronchoconstriction. H2 receptor blockade in vitro prevents the normal negative feedback of histamine on further mediator release in antigen challenge. Bronchospasm in guinea pigs given antigen challenge is enhanced by previous administration of metiamide or burimamide but not of cimetidine. These findings suggest the possible deleterious effect of H2 receptor antagonists in asthmatic subjects. The effects of H2 receptor blockade with cimetidine on bronchial hyperreactivity to histamine were studied in 10 asthmatic volunteers by whole body plethysmography. Cimetidine 800 mg and placebo were administered orally on two separate days, eight hours and two hours before study. No significant difference in baseline levels of airways obstruction was seen with the two agents. Inhalational challenge with increasing concentrations of histamine revealed no significant difference in bronchial hyperreactivity to histamine between cimetidine and placebo treatment days. H2 receptor blockade with cimetidine does not appear to affect ventilatory function or bronchial hyperreactivity to histamine in asthmatic subjects. It has been suggested that cimetidine may have H1 as well as H2 receptor blocking properties which prevent this effect.

The role of histamine in the pathogenesis of bronchial asthma remains controversial. Histamine is released from the lungs of asthmatic patients both in vitro¹ and in vivo² on appropriate allergen challenge while raised plasma histamine levels are found in spontaneously occurring asthmatic attacks.^{3,4} Bronchial hyperreactivity to inhaled histamine⁵ is prevented by H1 receptor blocking agents given parenterally⁶ and by inhalation.^{7,8} While orally administered H1 blockers are clinically ineffective in asthma, when given by inhalation, such agents are potent bronchodilators.⁹ These findings suggest that histamine acting on H1 receptors in the bronchi is important in the pathogenesis of the asthmatic attack.

The importance of the H2 receptor is less clear. Histamine added to leucocyte preparations has been shown to inhibit mediator release induced by antigen exposure.¹⁰ This effect is abolished by previous administration of the H2 receptor blocker metiamide.^{11,12} This suggests that the H2 receptor provides a negative feedback loop to limit further

mediator release. In vitro, histamine causes bronchial smooth muscle contraction but in the presence of H1 receptor blockade, histamine causes dose related smooth muscle relaxation which is abolished by H2 receptor blockade.¹³ These findings suggest that H2 receptor stimulation by histamine released from mast cells may limit the severity of asthmatic reactions both by a direct effect on bronchial smooth muscle and by limitation of further mediator release. Conversely H2 receptor blockade, while therapeutically useful in the reduction of gastric acid secretion, might enhance asthmatic attacks or lead to increased bronchial hyperreactivity.

This study was undertaken to ascertain if H2 receptor blockade would affect bronchial hyperreactivity to inhaled histamine.

Methods

Ten subjects, seven men and three women with an age range of 23-30 years (mean 26 years) gave informed consent. All gave a history of asthma with characteristic attacks but were in a stable

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clinical state at the time of study. Eight subjects had positive prick skin tests to more than one allergen. No subject was receiving oral corticosteroids or disodium cromoglycate. All were asked to abstain from bronchodilators and inhaled corticosteroids for 12 hours before each study. No subject had taken antihistamines within one week of study.

Subjects ingested cimetidine 800 mg or placebo eight hours and two hours before each study. These were administered double-blind and in random sequence for the two days.

Each study involved measurement of airways resistance (Raw) and thoracic gas volume (Vtg) by whole body plethysmography using a constant volume plethysmograph.¹⁴ Specific airways conductance (sGaw) was determined according to the equation $sGaw = 1/(Raw \times Vtg)$.

Baseline values of forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), and maximum expiratory flow at 50% of vital capacity (MEF₅₀) were measured using a McDermott spirometer, a stereo tape recorder, and a Hewlett Packard 9830 programmable calculator.^{15 16} The means of the three most technically satisfactory recordings of each measurement were obtained.

After baseline measurements of sGaw, FEV₁, FVC, and MEF₅₀, subjects inhaled increasing concentrations of histamine at three-minute intervals from a Hudson nebuliser. The concentrations were 0.1, 0.25, 0.5, 1.0, 2.5, 5.0, 10, 25, 50, 100, 250, and 325 mg/ml. Five tidal breaths of each concentration were taken and sGaw was measured before each concentration increment.¹⁷ This was continued until patients experienced wheezing and there was a 50% fall in sGaw from the baseline. At the end of the challenge sequence relief of bronchospasm was provided by the inhalation of salbutamol 200 µg.

Baseline values of FEV₁, FVC, MEF₅₀, and sGaw after cimetidine and placebo were compared using Student's *t* test for paired observations. Cumulative dose-response curves for histamine were constructed for each patient with each challenge and the mean percentage fall in sGaw at each histamine concentration calculated. The values found on cimetidine and placebo treatment days were compared by the same statistical test.

Results

There was no significant difference between mean values of FEV₁, FVC, MEF₅₀, or sGaw obtained after cimetidine or placebo. Oral cimetidine

800 µg did not alter airways obstruction at rest (table 1).

Inhalation of histamine caused a fall in sGaw in all patients on both treatment days (table 2, fig 1).

The mean percentage fall in sGaw for each histamine concentration was obtained for cimetidine and placebo treatment days. No significant

Table 1 Mean \pm SD for FEV₁, FVC, and MEF₅₀ after cimetidine and placebo

| | FEV ₁ (l) | FVC (l) | MEF ₅₀ (l/s) | sGaw (s ⁻¹ kPa ⁻¹) |
|------------|----------------------|-----------------|-------------------------|---|
| Cimetidine | 3.75 \pm 0.62 | 4.62 \pm 0.80 | 4.32 \pm 1.15 | 1.44 \pm 0.11 |
| Placebo | 3.72 \pm 0.77 | 4.63 \pm 0.89 | 4.18 \pm 1.38 | 1.50 \pm 0.11 |
| | NS | NS | NS | NS |

Table 2 Specific airways conductance (mean \pm SE) with histamine challenge

| Histamine concentration (mg ml ⁻¹) | Placebo (s ⁻¹ kPa ⁻¹) | Cimetidine (s ⁻¹ kPa ⁻¹) |
|--|--|---|
| Baseline | 1.50 \pm 0.11 | 1.44 \pm 0.11 |
| 0.1 | 1.42 \pm 0.15 | 1.32 \pm 0.12 |
| 0.25 | 1.42 \pm 0.14 | 1.37 \pm 0.12 |
| 0.5 | 1.43 \pm 0.15 | 1.23 \pm 0.14 |
| 1.0 | 1.23 \pm 0.10 | 1.12 \pm 0.14 |
| 2.5 | 0.88 \pm 0.13 | 0.86 \pm 0.15 |
| 5.0 | 0.73 \pm 0.15 | 0.66 \pm 0.11 |
| 10.0 | 0.61 \pm 0.19 | 0.47 \pm 0.22 |

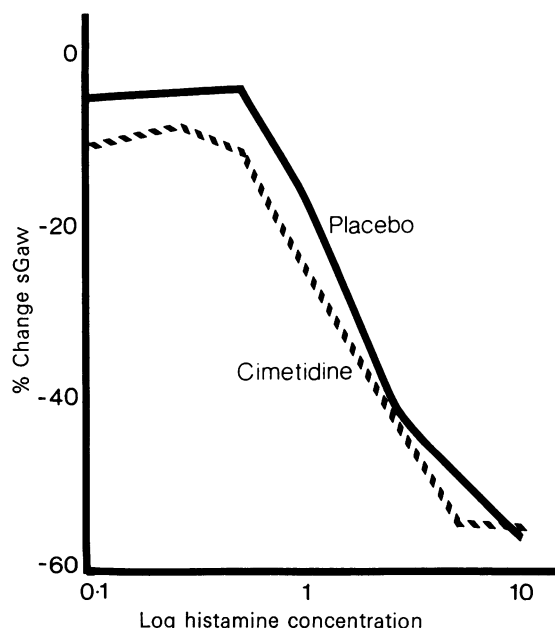


Figure Cumulative log dose-response curves to histamine with cimetidine and placebo.

differences were found between the effect of the two treatments at any histamine concentration. Thus the administration of cimetidine did not prevent or enhance histamine-induced bronchoconstriction in these subjects.

Discussion

In vitro studies suggest that the H₂ receptor has a role in the modulation of mechanisms involved in asthmatic attacks. Exogenous histamine has been shown to inhibit the release of histamine from leucocytes and this effect is blocked by H₂ receptor blockade with burimamide and metiamide.¹² The effect is thus thought to be the result of H₂ receptor stimulation and is associated with a rise in cyclic adenosine monophosphate.¹⁰ Such a use is also seen when a specific H₂ receptor agonist, demaprit, is given.¹⁸ H₂ receptor blockade with metiamide has been shown to potentiate histamine release induced by anti IgE in monkeys previously sensitised to IgE.¹⁹ The H₂ receptor may also have a role in modulating the effect of histamine on bronchial smooth muscle. H₁ receptor blockade leads to histamine-induced bronchodilatation which is abolished by metiamide.¹³

H₂ receptor blockade might be expected to lead therefore to enhanced mediator release and unopposed H₁ receptor-induced smooth muscle contraction. Earlier in vivo studies have failed to show this effect. Asthmatic subjects given cimetidine and placebo in a four-week crossover study showed no change in clinical state determined by daily peak flow measurements and symptom scores. There was no change in the severity of exercise-induced asthma in these patients when given cimetidine.

Inhaled histamine causes bronchoconstriction by a direct effect on bronchial smooth muscle and mucosa, and by stimulation of irritant receptors leading to vagally mediated reflex bronchoconstriction.^{20, 21} From the in vitro results it seems likely that the effect of inhaled histamine might be modulated by H₂ receptor stimulation leading to inhibition of endogenous mediator release and to bronchodilatation produced by H₂ receptor stimulation in bronchial smooth muscle. Our study, however, also failed to demonstrate any such H₂ receptor effect. Cimetidine-induced H₂ receptor blockade did not cause any increase in resting levels of airways obstruction or increase bronchial hyperreactivity to histamine.

This discrepancy between in vitro studies with metiamide and burimamide, and in vivo studies

with cimetidine could simply be the result of dosage and route of administration. H₁ receptor antagonists given by inhalation⁹ or in large parenteral dosages²² have bronchodilator properties which are not evident when given orally in conventional doses. Cimetidine given as a single oral dose of 400 mg has been shown to block gastric H₂ receptors and to inhibit gastric acid secretions.²³ While it could be argued that this is a local gastric effect, parenteral cimetidine given in sufficient dosage to achieve similar blood levels also results in the suppression of gastric acid secretion. Our dose of 800 mg would therefore have achieved blood levels sufficient to block gastric H₂ receptors although it is conceivable that blockade of bronchial receptors was not attained.

An alternative explanation has recently been suggested.²⁴ The lungs of guinea pigs previously sensitised to ovalbumen were excised after rechallenge and the increase in gas volume was taken as an index of the severity of the reaction. Pre-treatment with burimamide and metiamide significantly increased the severity of the reaction but this effect was not seen with cimetidine. On the other hand, cimetidine, but not burimamide or metiamide, significantly reduced the response to subcutaneous histamine. These findings suggest that cimetidine may differ from other H₂ receptor antagonists in having some H₁ receptor blocking activity. Thus while H₂ receptor blockade might enhance mediator release associated H₁ receptor blockade might prevent the resultant bronchoconstriction. Further support for this view is provided by the finding of an added protective effect when cimetidine is given with an H₁ receptor antagonist to prevent passive cutaneous anaphylaxis in monkeys.²⁵ Other workers, however, have failed to demonstrate any significant H₁ receptor blockade with cimetidine.²⁶

Cimetidine does not appear to have any significant effect on the bronchial hyperreactivity or ventilatory function of asthmatic patients. Further studies using more specific H₂ receptor antagonists in larger doses and by inhalation in spontaneous and induced asthmatic attacks may help clarify the role of H₁ and H₂ receptors in the human bronchus.

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