Histamine Blocking Agents in Healthy and Asthmatic Subjects*

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We compared the effects of two histamine receptor blocking agents, chlorpheniramine (H₁) and cimetidine (H₂), on the airways of healthy and asthmatic subjects. Eleven healthy subjects and ten asthmatic patients underwent histamine aerosol challenge. A threshold dose (T) for response to histamine was determined for each subject using maximal expiratory flow rates on partial expiratory flow volume curves (MEF40 %[P]). On subsequent study days, the subjects were pre-treated with 8 mg of chlorpheniramine, 300 mg of cimetidine or a lactose placebo. Histamine challenge was performed two hours later with the individual's own T dose and doses one dilution below (T–1) and one dilution above (T+1) that dose. In both asthmatic and healthy subjects chlorpheniramine significantly reduced the bronchoconstrictor responses to histamine (p < 0.02 and 0.05, respectively) as measured by MEF40 percent (P) at the T dose. When treated with cimetidine asthmatic patients displayed significantly more bronchospasm at T than with placebo (p < 0.035). By contrast, pretreatment with cimetidine did not alter airway responses to histamine in healthy subjects when compared to placebo. We conclude that H₂ receptors mediating bronchodilatation can be demonstrated in asthmatic patients but not in healthy subjects.

Histamine exerts its effects through interactions with at least two identifiable receptors (H₁ and H₂). Studies in animal models demonstrate that these receptors may play a role in induced as well as naturally-occurring bronchospasm. In vitro studies involving human airways have revealed the presence of H₁ and H₂ receptors. In vitro studies in asthmatic patients suggest that H₁ receptors mediate bronchospasm and H₂ receptors mediate bronchodilatation. In healthy subjects, a number of studies have revealed the presence of H₁ receptors, but the role of H₂ receptors has been difficult to document. A recent study in healthy subjects suggests the presence of both H₁ and H₂ receptors; however, the H₂ receptors in these subjects mediated bronchoconstriction rather than bronchodilatation.

Asthmatic subjects have been shown to be more sensitive to inhaled histamine than healthy subjects. Recent in vitro work suggests decreased H₂ receptor responsiveness in asthmatic patients and healthy subjects with viral infections. This has led some workers to postulate that increased airway reactivity in patients with asthma may in part be the result of an H₂ receptor deficiency. Whether differences in histamine receptors between asthmatic and healthy subjects contribute to differences in airway reactivity remains unknown. The purpose of this study was to compare the role of histamine receptors in histamine-induced bronchospasm in healthy and asthmatic subjects as measured by the effects of H₁ and H₂ receptor blocking agents.

METHODS AND MATERIALS

Eleven healthy subjects and ten asthmatic subjects were recruited as paid volunteers. All subjects gave informed consent, as approved by the Yale University Human Investigations Committee. Asthmatic subjects were selected on the basis of criteria established by the American Thoracic Society. Healthy subjects had no history of asthma or recent respiratory diseases and specifically denied clinical allergic diseases such as hay fever. Baseline pulmonary function parameters were essentially normal for the healthy subjects and revealed mild obstruction for the asthmatic subjects (Table 1).

Histamine dihydrochloride (Sigma, St. Louis) was prepared in normal saline as a solution of 128 mg base per ml and was kept frozen when not in use. Serial dilutions of the solution provided concentrations from 0.1, to 128 mg/ml (9 × 10⁻⁴ to 1.15M; pH=7.0 to 3.7). The lower concentrations (up to 0.4 mg/ml) were used for asthmatic subjects and the higher concentrations were used in healthy subjects. The histamine solution was delivered via a Dufterbande D-30 nebulizer, driven by 20 pounds per square inch of compressed air (0.05 ml liquid nebulized/min). A single nebulizer was used throughout the course of the experiment. The average particle size delivered by the D-30 nebulizer is less than 0.5 microns. This assures penetration of the histamine aerosol to the smaller airways. Histamine challenge was performed at the same time of day for each subject to control for diurnal variation. During each challenge the subjects wore a noseclip and inhaled the histamine through a mouthpiece attached to a separate, valved breathing circuit. The histamine aerosol was inhaled.

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Manuscript received October 12; revision accepted January 15.
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for 30 seconds by tidal breathing. Adverse symptoms to inhaled histamine at the highest challenge doses included headache, cough, flushing of the skin, tachycardia, and chest tightness. None of our subjects complained of sore throat or hoarseness. Higher doses of histamine were not given to subjects after the onset of adverse symptoms.

All drugs were administered orally in a single blind fashion. These included the H1 receptor antagonist, cimetidine (300 mg) (Smith, Kline, and French, Philadelphia), the H2 receptor antagonist chlorpheniramine maleate (8 mg) (USV, Tuckahoe), and a lactose placebo (Eli Lilly and Company, Indianapolis). Medications were administered, one and a half to two hours prior to histamine challenge.

Subjects performed forced vital capacity maneuvers using a pneumotachograph-integrator system;20 they inhaled to approximately 50-70 percent of their vital capacity, and then exhaled as fast as possible to residual volume, thereby generating a partial expiratory flow-volume (PEFV) curve.21 The subjects next inhaled to total lung capacity and exhaled as fast as possible to residual volume, generating a maximal expiratory flow-volume (MEFV) curve. A programmable marker, set to trigger at 1 second, permitted identification of the forced expiratory volume at 1 second (FEV1). The resultant curves allowed measurement of the forced vital capacity (FVC), peak expiratory flow rate (PEFR) and maximum expiratory flow rates at 60 percent of the vital capacity, below total lung capacity on the MEFV curve (MEF40%), and PEFV curve (MEF40%(P)). Histamine challenge was performed as previously described. The response to the inhalation of histamine was followed by pulmonary function testing at 0, one, two, four, six and eight minutes following a given challenge. The average of the first three and second three blows were calculated. Bronchospasm did not result from repeated FVC maneuvers, presumably because of the pause between maneuvers.

If a subject did not experience a 20 percent fall in MEF40 %(P) for a given dose of histamine then the next dose was administered after a 30-minute wait. The MEF40%(P) was used to define the threshold dose in this study because it was a more sensitive measure of airway obstruction and permitted us to observe significant bronchospasm at lower histamine doses than would have been possible with the FEV1 (Fig 1). The wait between successive doses of histamine was used to control against any cumulative effects of histamine.22 The dose at which at least a 20 percent fall in MEF40 %(P) occurred was designated the threshold (T) dose.

The study took place on four separate days. On the first day, a histamine dose response challenge was performed to establish a threshold dose (T). On each of the subsequent three drug days, subjects were challenged sequentially with histamine doses corresponding to T-1 (one dose below threshold), T (threshold) and T+1 (one dose above threshold) two hours after taking the drug. Baseline pulmonary function was determined at the beginning of each of the four study days (Table 2). Baseline pulmonary function of all four days were compared using Hotelling’s T2 test on repeated measurements.23 Comparisons between lung function changes on each of the drug days for each of the three histamine doses was performed by paired t-test in both healthy subjects and asthmatic patients.24

**RESULTS**

Analysis using Hotelling’s T2 test on repeated measurements of the baseline FEV1 and MEF40 %(P) for each study day (Table 2) demonstrated that baseline pulmonary function did not significantly vary from day to day in both healthy subjects and asthmatic patients. Nevertheless, a slight trend of better function on drug and placebo days can be seen among asthmatic subjects, compared to the day on which no drug was used.

Dose response curves were generated for histamine challenge in asthmatic and healthy subjects.

### Table 1—Anthropometric Data in Asthmatic and Nonasthmatic Subjects (Mean ± ISD)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age</th>
<th>Sex</th>
<th>FVC (L)</th>
<th>FEV1 (L)</th>
<th>FEV1, %</th>
<th>PEFR (L/sec)</th>
<th>MEF 50% (L/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthmatic</td>
<td>27.4 ± 7.9</td>
<td>8F, 2M</td>
<td>3.39 ± .80</td>
<td>2.56 ± .74</td>
<td>75.1 ± 15.57</td>
<td>5.43 ± 1.59</td>
<td>2.69 ± .99</td>
</tr>
<tr>
<td>% Predicted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthmatic</td>
<td></td>
<td></td>
<td></td>
<td>81%</td>
<td>76%</td>
<td>93%</td>
<td>76%</td>
</tr>
<tr>
<td>% Predicted</td>
<td></td>
<td></td>
<td></td>
<td>89%</td>
<td>94%</td>
<td>96%</td>
<td>93%</td>
</tr>
</tbody>
</table>

### Table 2—Comparison of Baseline Pulmonary Function on Four Protocol Days (Mean ± SEE)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Protocol Day</th>
<th>No Drug</th>
<th>Chlorpheniramine</th>
<th>Cimetidine</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthmatic</td>
<td>MEF40%(P) (L/sec)</td>
<td>1.91 ± .32</td>
<td>2.40 ± .36</td>
<td>2.34 ± .37</td>
<td>2.34 ± .44</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>FEV1 (L)</td>
<td>2.49 ± .75</td>
<td>2.81 ± .68</td>
<td>2.88 ± .73</td>
<td>2.72 ± .74</td>
<td>NS</td>
</tr>
<tr>
<td>Nonasthmatic</td>
<td>MEF40%(P) (L/sec)</td>
<td>3.61 ± .31</td>
<td>3.77 ± .35</td>
<td>3.56 ± .37</td>
<td>4.31 ± .50</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>FEV1 (L)</td>
<td>3.77 ± .20</td>
<td>3.73 ± .17</td>
<td>3.73 ± .19</td>
<td>3.81 ± .26</td>
<td>NS</td>
</tr>
</tbody>
</table>
In Figure 1 we contrast results seen with FEV\textsubscript{1} and MEF40\% (P) measurements. The effects of histamine on pulmonary function for each group became significantly different from baseline at the T-1 histamine dose for MEF40\% (P) and at the T histamine dose for FEV\textsubscript{1}. At each dose of histamine, the MEF40\% (P) was a more sensitive measurement of bronchoconstriction than the FEV\textsubscript{1}. The average histamine dose at threshold was 37.8 ± 17.0 mg/ml for the nonasthmatic subjects and 54 ± 1.0 mg/ml for asthmatic patients. In all subsequent analyses, results will be reported for the MEF40\% (P) alone. Asthmatic patients (Fig 2), when pretreated with cimetidine, had decreases in pulmonary function following T which were significantly greater than those following placebo (p < .035). Among asthmatic patients, pulmonary function following pretreatment with chlorpheniramine was significantly better than placebo (p < .02) or cimetidine (p < .004) at the T dose. A significant placebo effect was observed (p < .01) when the placebo day was compared to the no drug day.

Among nonasthmatic subjects (Fig 3), the effect of cimetidine was no different from that of the placebo. Chlorpheniramine prevented the decline in MEF40\% (P) at the T dose of histamine when compared to the day on which no drug was administered (p < .002), the day on which placebo was administered (p < .05) and the day on which cimetidine was administered (p < .03). No significant placebo effect was observed in these nonasthmatic subjects.

**Discussion**

Pretreatment of asthmatic subjects with cimetidine significantly increased airway obstruction following inhalation of histamine, when compared to non-asthmatics.

**Figure 2.** The effects of pretreatment with antihistamines on inhaled histamine at the T-1, T and T+1 dose levels in nonasthmatic subjects measured as a percentage of the pre-inhalation baseline (MEF40\% (P)). Significance levels refer to comparisons at a given histamine dose between placebo day measurements and measurements on the other drug days.
placebo. By contrast, healthy subjects did not alter their response to histamine aerosol when pretreated with cimetidine. These findings suggest the presence of H₂ receptors mediating bronchorelaxation in the airways of asthmatic patients but not in the airways of healthy subjects. The comparisons used to establish these contrasts involve the difference between drug day and placebo day. It should be noted that for the asthmatic subjects there was no difference between challenge with T on the cimetidine day and the no-drug day. We interpret this finding to mean that the bronchoconstrictor effect of cimetidine is equal in magnitude, but opposite in direction to the placebo effect observed in asthmatic patients. It is possible, but we feel unlikely, that cimetidine works through an independent mechanism to abolish the placebo effect which is unrelated to histamine receptors. More likely, the effect of cimetidine is unrelated to the placebo effect. By contrast, if H₂ receptors are present in the airways of healthy subjects, the effects of H₂ receptor antagonism on histamine-induced airway constriction are negligible. Taken together, these results suggest a possible difference between asthmatic and healthy subjects in either the absolute number, distribution or sensitivity of airway H₂ receptors.

Our findings in asthmatic patients are consistent with those of Nathan et al.¹⁵ who showed a significant bronchoconstricting effect of H₂ blockade on subsequent histamine challenge in asthmatic patients. By contrast, Eiser¹² reported that H₂ blockade in asthmatic patients shifts the histamine dose-responsive curve to the right.

The finding that cimetidine has no significant bronchoconstricting effect in nonasthmatic subjects is consistent with the preliminary reports of Eiser et al.⁸ Macnachnie and Wooddings,⁹ and Nilsson et al.¹⁰ However, our findings in healthy subjects are in conflict with the study of Eiser et al.,¹² in which administration of 400 mg of oral cimetidine was shown to have a mild protective effect against inhaled histamine.

The finding that cimetidine promotes bronchospasm in asthmatic patients but not healthy subjects could be due to the fact that cimetidine is not displaced by the low levels of histamine used in sensitive individuals. An alternate explanation might be related to the location of histamine receptors in the airways. Yen et al.²³ have shown that H₂ receptors are more active in the central airways than in the peripheral airways of the guinea pig. If the H₂ receptors are abundant in small airways in asthmatic patients but not in those of healthy subjects, the preferential distribution of the very fine aerosol of a D-30 nebulizer to the smaller airways could explain the differences seen in this protocol. Finally, differences in histamine receptor responsiveness could also explain the findings in this study. Busse et al.¹⁴ found H₂ receptors to be less responsive in asthmatic patients than healthy subjects in their ability to inhibit lysozymatic enzyme release from granulocytes.

As expected, chlorpheniramine had a very significant effect in preventing histamine-induced bronchoconstriction in both asthmatic and nonasthmatic subjects. However, it can be seen from the comparison of baseline pulmonary function from each day that chlorpheniramine, cimetidine, and placebo each had no significant bronchoconstricting effects on resting airway tone (Table 2), although a mild placebo effect is suggested by the trend in asthmatic patients.

In conclusion, the experimental evidence presented in this investigation suggests differences in H₂ receptor function in the airways of healthy and asthmatic subjects. These receptors appear to mediate bronchodilatation in asthmatic patients and can be blocked by cimetidine. Under the conditions of this protocol, the role of H₂ receptors in the airways of healthy subjects appears to be negligible.

ACKNOWLEDGMENT: The writers wish to thank Dr. Gerald J. Beck for his helpful suggestions in the statistical analysis of our data as well as Martha Krill and Miriam Tofig for typing the manuscript.

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The first convention of the Societas Europaea Pneumologica will be held in Bruges, Belgium, September 15-22. The meeting will be divided into three parts: 1) Lung Carcinoma in Europe (September 16-18); 2) separate meetings of different sections of the Society (September 20-21); and 3) postgraduate courses. Members of the Executive Committee are: Drs. R. Panner, Belgium, President; D. Flenley, United Kingdom; H. Herzog, Switzerland, Vice-Presidents; R. Bollinelli, France, Secretary-General. For information, write the Secretariat-General: PO Box 2065, CH-8035 Zurich 35, Switzerland.