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Modulation of histamine-induced bronchoconstriction with inhaled, oral, and intravenous clemastine in normal and asthmatic subjects

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ABSTRACT Although histamine plays an important role in the pathophysiology of asthma through stimulation of H1 receptors, H1 antagonists are of only limited use in this disease when given orally. In order to investigate the pharmacological response to a specific H1 antagonist administered by different routes, we measured the effect of inhaled clemastine on airway responsiveness to histamine aerosol and compared the results with those after oral and intravenous administration in normal and asthmatic subjects. Inhalation of 0·6 mg clemastine provided significant protection without side effects and was comparable to intravenous administration of 1·0 mg in both groups. In normal subjects 2·0 mg clemastine orally was significantly less effective than the two other routes of administration whereas in asthmatics an enhanced reaction to histamine was observed.

The role of histamine in experimental hypersensitivity and clinical allergic states has become well established.[1-3] There is now ample evidence that the pathophysiological effects of histamine in asthma result from the stimulation of H1 receptors[4] which are modulated by the presence of H2 receptors.[5] However H1 antihistamines are of only limited use in the therapy of asthma,[6] and this may be the result of insufficient local drug concentration when given orally. Recently it was shown that aerosol clemastine causes bronchodilation comparable to salbutamol[7] and protects against histamine-induced bronchospasm.[8] Partidge *et al*[9] could not confirm bronchodilation after clemastine and did not find it therapeutically useful in the long-term treatment of asthma. We feel that these apparent contradictions may have been partly due to the different dosages used and we therefore studied the effect of inhaled clemastine on histamine-induced bronchospasm using a dose-response analysis. To our knowledge no dose-response study is available relating the amount of aerosol clemastine to airway response induced by inhaled histamine. These results were then compared with the effect of oral and intravenous administration of clemastine on aerosol histamine in healthy and asthmatic subjects in order to investigate the role played by mode of administration.

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Methods

Five healthy volunteers (mean age 25 years; range: 19-31 yr) with no history of pulmonary disease were studied. In addition five patients with extrinsic asthma (mean age 26 years; range 22-30 yr) were selected. All asthmatics were outpatients and had previously been shown to have reversible airways obstruction during the pollen season. All had positive skin tests to grass pollen and elevated total and specific IgE levels. At the time of the study, which was outside the pollen season, all asthmatics were symptom-free and on no drug therapy. Except for one subject all lung function data were within normal limits. The subjects had given informed consent to the experimental protocol.

Histamine and clemastine were delivered by high pressure nebuliser (Heyer Piccolo, Bad Ems, West Germany) generating an aerosol of mass median diameter from 1·5 to 4·5 microns. The different dosages of histamine and clemastine, dissolved in 1·5 ml saline or buffered solution respectively, were inhaled with tidal breaths over a time period of about three minutes. Lung function determined before and three and 10 minutes after histamine inhalation, was assessed by spirometry (forced expiratory volume in one second, FEV_1) with a Fleisch no 3 pneumotachograph (Fenyves and Gut, Basle, Switzerland).

In a cumulative fashion we first determined the dose of histamine which caused a decrease of FEV_1

of more than 25%. The next day, the final dose of histamine was inhaled again and referred to as the provocation dose. In all healthy subjects and in two asthmatics, this dosage was inhaled on five different days in order to evaluate reproducibility. The coefficient of variation was found to range between 20 and 30%. The provocation dose thus determined was used throughout further testing and the resulting changes in lung function taken as reference values. Inhalation of saline was performed in all subjects to detect non-specific reactors.

In order to relate the amount of aerosol clemastine to the airway response induced by inhaled histamine 0·1, 0·3, 0·6, and 1·0 mg of clemastine were inhaled 10 minutes before the histamine provocation dose in five healthy subjects.

On separate days, the effects of clemastine given orally as a single 2·0 mg dose four hours before histamine inhalation, intravenously (1·0 mg) and by inhalation (0·6 mg) both 10 minutes before histamine challenge, were compared. This study was performed in all subjects.

Statistical analysis was carried out using Student's *t* test for paired values.

As clemastine, irrespective of the mode of administration, did not significantly change the baseline values, and as the change obtained three minutes after histamine was consistently higher than that at 10 minutes, we compared only the three-minute values after histamine with those before challenge. The difference was considered significant at the $p < 0.05$ level.

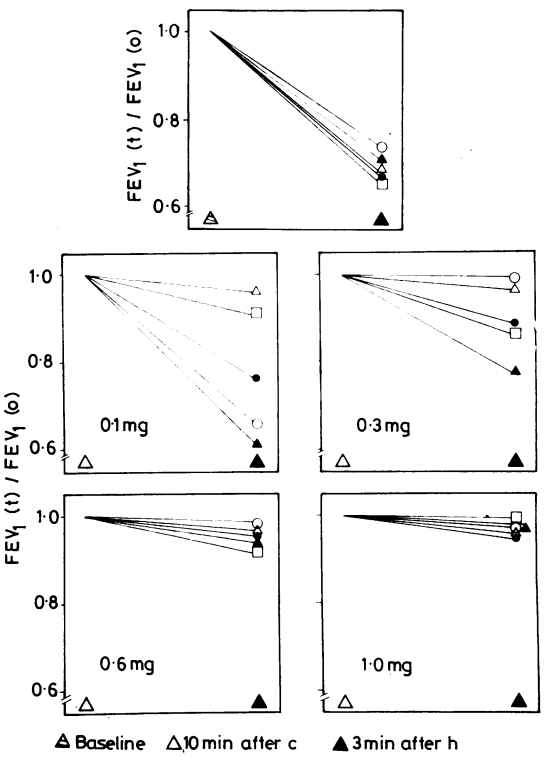

Fig 1 *Inhaled clemastine dose response. FEV_1 before and three minutes after challenge. Above: histamine challenge without clemastine. Below: histamine challenge after inhalation of 0·1, 0·3, 0·6, and 1·0 mg clemastine.*

Results

The histamine dosages (mean ± standard deviation) used were 4·2 ± 2·2 mg in normal subjects and were significantly higher than those used in asthmatics (1·4 ± 1·5 mg). The observed difference is in agreement with published reports.[18 19] The recorded changes in FEV_1 after histamine were comparable in the two groups, with a mean change (± standard deviation) from 3·6 ± 0·3 to 2·5 ± 0·1 l in normal and from 3·7 ± 0·9 to 2·5 ± 0·8 l in asthmatic subjects.

In five subjects inhalation of 0·1, 0·3, 0·6, and 1·0 mg clemastine respectively altered the airway response in a dose-related way. In fig 1 the data are expressed in terms of FEV_1 and compared with the histamine provocation without previous clemastine inhalation. As 1·0 mg did not provide additional protection from histamine challenge, 0·6 mg clemastine were used throughout the further studies as an amount with sufficient H1 antagonist activity to interfere with histamine stimulation.

In fig 2 the effects of the three modes of administration of clemastine on histamine challenge are presented in terms of the relative change of FEV_1. The percent change in FEV_1 was 18·0 ± 10·6 (mean ± standard deviation) after oral administration, 5·0 ± 1·6 after inhalation, and 3·0 ± 2·7 after injection. Without treatment histamine produced a change in FEV_1 of 30·2 ± 3·2. Therefore irrespective of the mode of administration, clemastine diminishes the effect of histamine ($p < 0.05$); however inhaled and injected clemastine are more effective than oral clemastine ($p < 0.05$).

In fig 3 the data obtained in the asthmatics are presented in the same manner as for the normals in fig 2. The percent change of FEV_1 was 49·9 ± 13·9 (mean ± standard deviation) after oral administration, 6·6 ± 7·3 after inhalation, and 4·7 ± 5·3 after injection. Without treatment histamine produced a change in FEV_1 of 37·9 ± 13·5. In the asthmatics, therefore, inhalation of 0·6 mg and injection of 1·0 mg clemastine significantly inhibits histamine-induced bronchoconstriction ($p < 0.05$).

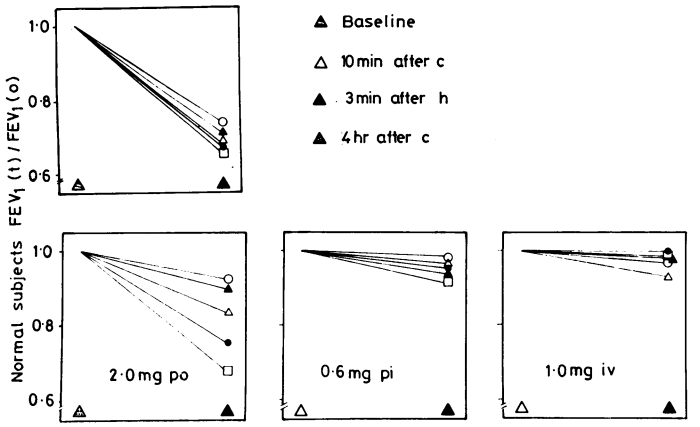

Fig 2 *Histamine challenge without clemastine (above) and with clemastine orally (po), by inhalation (pi) and intravenously (iv) (below) in normal subjects. Percent change of FEV_1 before and three minutes after challenge.*

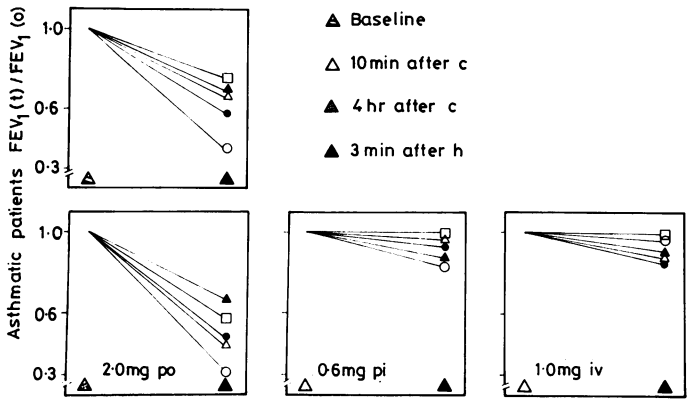

Fig 3 *Histamine challenge without clemastine (above) and with clemastine orally, by inhalation, and intravenously (below) in asthmatic subjects. Percent change of FEV_1 before and three minutes after challenge.*

However oral clemastine enhances the histamine-induced bronchospasm significantly ($p < 0.05$) when compared with the challenge without the drug.

Discussion

In this study we have demonstrated that the specific H1 antagonist clemastine diminishes the bronchoconstrictor effect of inhaled histamine. The protective activity is both dose-related and dependent on the mode of administration. The dosage used for intravenous injection and inhalation were equally effective in blocking histamine-induced bronchoconstriction in normal and asthmatic subjects, whereas oral administration was effective only in normal subjects and to a lesser degree. Since clemastine does not possess significant anticholinergic or antiserotonin properties,[10] the observed effects can be attributed to specific anti-H1 activity.

The idea of increasing the therapeutic efficacy of antihistamines through inhalation was first put forward over 30 years ago. However, despite encouraging results[11–13] the subject was not pursued. Recently the effects of clemastine,[7–9] chlorpheniramine,[14] and diphenhydramine,[15] all given by inhalation, have been studied. A protective effect from histamine challenge comparable to that observed by us was demonstrated by all these investigators.

To evaluate the interaction of an agonist or antagonist with an assumed receptor, variability of the receptor response to the stimulus should be known. The inter-individual variability was similar than that reported in the literature.[15,16] A critical part of the experimental protocol is the dosage of clemastine used and the time schedule of lung function determinations. The rationale for our protocol was as follows: (a) clemastine 2·0 mg orally and 1·0 mg intravenously are doses usually considered within the therapeutic range used for allergic disease. (b) Clemastine 2·0 mg orally gives peak serum levels (2 ng/ml) after four hours when given as a single dose, whereas 1·0 mg clemastine

intravenously gives peak serum levels (4 ng/ml) after 10 minutes.[17] Since we did not perform any pharmacokinetic measurements, we cannot exclude deviations in our subjects from the data obtained by Tham *et al.*[17] (c) The choice of inhaled dosage and the time schedule was based on the results obtained in the dose-response study. The dose used was in the range used by Nogrady *et al.*[7 8]

From the results obtained, it is reasonable to suggest that the lesser degree of protection achieved by oral as opposed to intravenous injection or administration by inhalation results from lower tissue concentration of the drug. If local drug concentration mainly determines the airway response, comparable tissue concentrations have to be assumed after inhalation and injection of clemastine despite differing dosages. The reasons for the enhanced reaction to histamine in asthmatics after oral medication are unclear. Several explanations could account for this paradoxical behaviour including variation in histamine sensitivity, modification of receptor sensitivity to histamine by clemastine or differences in drug absorption and tissue concentration of both the agonist and the antagonist. Whatever the explanation, the difference in response to histamine with low concentrations of clemastine between normal and asthmatic subjects remains an interesting observation.

Intravenous and oral medication, the latter to a lesser degree, caused disturbing sedation or drowsiness whereas no side-effects were reported after inhalation of the drug. Furthermore an attempt to improve the efficacy of oral clemastine by dosage increment would lead to increased and ultimately intolerable side-effects as already pointed out for other antihistamines by Schild *et al.*[18] It is therefore clear that the clinical use of both intravenous and oral clemastine is limited by its side-effects.

We conclude from this study, that inhalation of 0·6 mg clemastine prevents histamine-induced bronchoconstriction in normal and asthmatic subjects without producing side-effects. The therapeutic inefficacy found by Partridge *et al*[9] may be based on patient selection and the relatively low dosages of clemastine used when compared with the results obtained from our dose response study. Further investigation of the therapeutic value of inhaled clemastine might therefore be of interest.

This study was presented in part at the Annual Meeting of the American College of Chest Physicians in Houston in 1979.

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