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Inhaled clemastine, an H_1 antihistamine inhibits airway narrowing caused by aerosols of non-isotonic saline

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Inhaled clemastine, an H_1 antihistamine, inhibits airway narrowing caused by aerosols of non-isotonic saline. L.T. Rodwell S.D. Anderson, J.P. Seale.
ABSTRACT: Asthmatic subjects were challenged with aerosols of hyper- and hypotonic saline 15 min (Group A) and 90 min (Group B) after inhaling clemastine. Measurements were made of forced expiratory volume in one second (FEV_1) before and after medication and after challenge. When the FEV_1 values (% predicted) were compared on the active and placebo days they were higher 15 min after clemastine ($p<0.05$) for both challenges and higher 90 min after clemastine inhalation ($p<0.05$) for the hypertonic challenge. The % fall in FEV_1 was compared after the same concentration of saline aerosol had been given on both active and placebo days. In Group A the % fall in FEV_1 on the clemastine day was reduced after challenge with hypertonic ($p<0.02$) and hypotonic ($p<0.03$) aerosol. In Group B there was a reduction in the % fall in FEV_1 on the clemastine day only after hypertonic challenge ($p<0.04$). The protective effect afforded by clemastine was unrelated to change in baseline lung function. We conclude that histamine is an important mediator of the airway response to non-isotonic aerosols and suggest that the aerosol route of administration may be useful for delivering antihistamines.
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It is now widely accepted that changing the osmolarity of the airways by inhaling non-isotonic aerosols is a potent stimulus for airway narrowing in subjects with asthma [1, 2]. The mechanism for this is not known although histamine is thought to be an important mediator of the response [3].

Histamine is a preformed mediator found only in human mast cells and basophils. As mast cells are located in bronchial mucosa and in the airway lumen of asthmatic subjects [4], they are in an ideal situation to release histamine and other mediators when exposed to a change in osmolarity; a stimulus to which they are known to be sensitive *in vitro* [5].

Recent studies demonstrated that the highly selective antihistamine terfenadine, when given orally, provided partial protection against challenge with hypo- and hypertonic aerosols of sodium chloride [3, 6, 7]. However, some airway narrowing still occurred, suggesting either that other mediators are involved or that the tissue concentration of terfenadine was insufficient to antagonize the action of histamine at all receptor sites. Terfenadine also induced bronchodilatation in some subjects, providing indirect evidence that histamine was contributing to resting airway tone.

The superiority of the aerosol route of administration of drugs has been recognized for many years, particularly in the treatment of exercise-induced asthma [8]. Aerosol delivery of drugs allows small doses to reach the airways in high concentrations and to have an immediate effect compared with oral administration.

The aim of this study was to examine the effect of an $histamine_1$ receptor antagonist, delivered as an aerosol, on responses to changes in airway osmolarity. We chose clemastine because it is available in an injectable form and can easily be nebulized. In addition, it has a high H_1 receptor specificity, low anti-cholinergic activity and a low incidence of central nervous system side-effects [9].

Materials and methods

Subjects

Fourteen subjects with clinically stable asthma were selected for the study on the basis of a reduction in their forced expiratory volume in one second (FEV_1) of at least 20% after a bronchial provocation challenge with hypertonic saline. Their anthropometric details, mean pre-challenge FEV_1 values, the concentration of saline required to provoke a 20% fall in FEV_1 (PC_{20}) to hypertonic saline on selection day, and regular medications are given in table 1. All subjects were tested with eight common allergens and all had at least one positive reaction as defined by a wheal size greater than 2mm.

Table 1. – Anthropometric details, mean pre-challenge values for FEV_1, regular medications, and PC_{20} (% saline) to hypertonic saline on selection day, for ashtmatic subjects who were challenged 1. 15 min - Group A; and 2. 90 min - Group B, after the administration of aerosol clemastine, its placebo or 0.9% saline

1. 15 min - Group A

Subject no	Age yrs	Sex	Height cm	Pred FEV_1 *l*	% Pred FEV_1 ±SD*	Medications	PC_{20}
6	20	F	166	3.31	85±3.6	B,S	2.1
8	20	F	163	3.21	128±6.3	B,S	3.0
9	30	F	164	2.74	76±2.6	–	4.0
10	19	F	172	3.59	91±3.9	B	5.3
11	28	M	170	3.97	81±5.7	B,S	6.6
13	18	M	180	4.36	86±11.4	B,S	5.7
14	21	F	167	3.32	90±5.6	B,D	4.0
15	19	F	161	3.20	81±4.8	B,D,I	2.4
$\bar{x}$±SD	22±4.5				90±16.2		

2. 90 min - Group B

Subject no	Age yrs	Sex	Height cm	Pred FEV_1 *l*	% Pred FEV_1 ±SD**	Medications	PC_{20}
1	27	M	180	4.66	72±4.4	B,S	3.8
2	30	M	184	4.94	94±2.9	B,S	3.7
3	58	M	175	3.42	80±2.4	–	4.0
4	25	M	188	5.22	70±2.7	B,S,D	8.2
5	25	M	171	4.12	92±4.1	B,S	6.1
6	20	F	166	3.31	80±12.2	B,S	2.1
7	36	M	191	5.13	88±4.0	B	4.0
10	19	F	172	3.59	94±3.2	B	5.3
$\bar{x}$±SD	30±12.5				84±9.7		

*: Mean of six FEV_1 measurements; **: Mean of eight FEV_1 measurements. Group B: mean for subject 10 is of 6 measurements. B: beta-adrenoceptor agonist; S: aerosol corticosteroid; D: cromolyn; I: Ipratropium bromide; FEV_1: forced expiratory volume in one second; PC_{20}: concentration of saline required to provoke a 20% fall in FEV_1.

Subjects were clinically well controlled with bronchodilators and/or inhaled corticosteroids and were able to manage without aerosols of $beta_2$-adrenoceptor agonists, or sodium cromoglycate for at least 6 h and ipratropium bromide for 10 h. Those subjects requiring aerosol steroids had not changed the dose for 8 weeks before the study or throughout the trial period. The subjects had no other chronic illness, recent chest infection or major antigen exposure in the previous 4 weeks.

After initial screening the subjects inhaled nebulized clemastine, or placebo, in a double blind cross-over design, either 15 min (Group A) or 90 min (Group B) before hypertonic, hypotonic, or histamine bronchial challenges. The study was approved by the Royal Prince Alfred Ethics Review Committee. Eight subjects were included in Groups A and B for the histamine and hypertonic challenges. Only 7 subjects were included in Group A for the hypotonic challenge because Subject No. 10 was not responsive to the hypotonic challenge.

Experimental design

The study, which comprised a minimum of seven visits to the laboratory for each subject, was carried out over a period of approximately two months. For each individual, visits occurred at approximately the same time of day to avoid any variability associated with circadian rhythms.

On arrival at the laboratory, spirometry (Minato Autospirometer AS500 or AS600, Osaka, Japan) was performed. Subjects were asked about recent symptoms of wheeze or dyspnoea. If subjects reported significantly increased symptoms within the last 24 h, the testing did not proceed.

On Day 1 a progressive hypertonic challenge of increasing tonicity (0.9%, 1.8%, 3.6%, 7.2%, 14.4%) was performed to select subjects for the study. Thus all subjects tested had a fall in FEV_1 greater than 20% from baseline value after the inhalation of hypertonic saline. Their PC_{20} had to be less than 8.5% saline to be included in this study. All subjects had a PD_{20} to histamine on the placebo day of less than 3.84 μmoles. On Days 2 and 3, subjects inhaled nebulized clemastine or placebo, either 15 min or 90 min prior to a histamine challenge [10]. On Days 4 and 5, clemastine or placebo were inhaled either 15 min or 90 min before progressive hypertonic challenges. On Days 6 and 7, inhalation of clemastine or placebo was followed either 15 min or

90 min by progressive hypotonic challenges (of decreasing tonicity, that is, 0.9%, 0.45%, 0.23%, 0.11%, 0.06%, and 0.03%).

A 90 min time period between clemastine inhalation and bronchial challenge was chosen on the basis of a previous study with inhaled clemastine [11]. In the second part of the study, the time interval was reduced to 15 min to assess whether clemastine had an earlier onset of action and a greater protective effect at this time.

Techniques and procedures

Histamine challenge (Days 2 & 3). Histamine challenges were carried out to assess the efficacy of inhaled clemastine in blocking histamine H_1-receptors. DeVilbiss No.40 glass hand-held nebulizers (Somerset, Penn, USA) were used to administer the histamine aerosol. The same nebulizer, the output of which had been carefully measured, was used to deliver each concentration of histamine throughout the study. The method used to deliver the histamine aerosol was developed by YAN *et al.* [10] although the maximum cumulative dose of histamine delivered to each subject was increased beyond that described in the original method to 6.5 μmoles. The time taken to perform the histamine challenge varied from 2–15 min.

The challenge was stopped when FEV_1 fell by more than 20% from the post-saline (0.9%) value, or when the maximum dose was reached.

Bronchodilators were administered at the completion of the challenge, either by a metered dose inhaler or *via* a jet nebulizer.

Non-isotonic aerosol challenge. The MistO_2gen Ultrasonic Nebulizer (Timeter, Penn, USA) was used to generate the hypertonic and hypotonic aerosols. Subjects inhaled the aerosols at resting ventilation rates through a two-way valve (Hans Rudolph 2700, Kansas City, Missouri, USA) and mouthpiece connected to the nebulizer by corrugated tubing 67.5 cm in length and an internal diameter of 22 mm. This unit was weighed (Sartorius 1216MP, Gottingen, Germany) before and after 3 min of nebulization. The amount of aerosol delivered over 3 min remained relatively constant between subjects (range 1–1.5 $ml \cdot min^{-1}$). The aerosol particle size delivered to the subjects through this circuit is approximately 3.6 micron and monodispersed [12]. For these aerosol characteristics between 15% and 35% of the volume leaving the mouthpiece is predicted to be deposited in the tracheobronchial region [13].

Hypertonic Aerosol Challenge (Day 1 and Days 4 & 5). Subjects commenced the challenge by inhaling an isotonic solution of saline (*i.e.* 0.9%) for 3 min. The FEV_1 was measured 3 min later and only two measurements were made if the subject's effort was satisfactory. During this 3 min period, before measuring spirometry, the solution in the nebulizer was replaced with progressively more concentrated saline solutions (1.8%, 3.6%, 7.2%, and 14.4%). If the FEV_1 had fallen less than 20% compared to pre-challenge FEV_1, the subject then inhaled aerosols of the next incremental concentration for a further three minutes. This procedure was repeated until a 20% fall in FEV_1 had been obtained or the 14.4% solution had been inhaled for 3 min. Bronchodilators were administered after completion of the challenge.

Subjects were required to have a fall in FEV_1 of greater than 20% of their prechallenge value for inclusion in the trial.

Hypotonic Aerosol Challenge (Days 6 & 7). This challenge followed the same procedure as the hypertonic challenge except that progressively more dilute saline solutions were placed in the nebulizer according to the sequence 0.9% saline (isotonic solution), 0.45%, 0.23%, 0.11%, 0.06% and 0.03%. The challenge ended once the FEV_1 had fallen greater than 20% compared to the pre-challenge FEV_1, or the 0.03% had been inhaled. Bronchodilators were administered as required after completion of the challenge.

Clemastine (1 $mg \cdot ml^{-1}$: dose nebulized approx. 0.5 mg). Ampoules of clemastine (2 $mg \cdot 2\ ml^{-1}$) were diluted with sterile water (1:3) in order to deliver to the subjects approximately 0.5 mg of clemastine. The placebo was the solvent for clemastine and was prepared by the Department of Pharmacy, Royal Prince Alfred Hospital after consultation with Sandoz. Two ml of this solvent was comprised of sorbitol (90 mg), ethanol (140 mg), propylene glycol (600 mg), and sodium citrate to bring the pH to 6.3. The osmolalities of the clemastine solution and placebo, as measured by vapour pressure osmometry, were 6870 $mOsmol \cdot kg^{-1}$ and 7316 $mOsmol \cdot kg^{-1}$ respectively. These were diluted with sterile water (1:3), making the osmolalities of the delivered clemastine and placebo 1604 $mOsmol \cdot kg^{-1}$ and 1733 $mOsmol \cdot kg^{-1}$ respectively. These solutions were still hyperosmolar compared to the estimated osmolality of the periciliary fluid *i.e.* 359 $mOsmol \cdot kg^{-1}$ [14]. For this reason the clemastine placebo (*i.e.* solvent) was compared with 0.9% saline to assess if the solvent had an effect on baseline lung function when administered before bronchial challenges, and if the solvent affected responses to the bronchial challenges performed. The 90 min histamine challenge was performed after the solvent and after 0.9% saline inhalation in order to assess these differences.

Delivery of clemastine to subjects. Updraft 1700 jet nebulizers with Y-shaped mouthpieces were used to deliver clemastine (or placebo). The nebulizers were driven by compressed air from a cylinder at a flowrate of 8 $l \cdot min^{-1}$. Under these conditions, the aerosol particle size is 3.5 micron [15]. In an attempt to maintain a constant aerosol particle size and solute concentration the nebulizer bowls were heated in a warm water bath (32°C–35°C) during nebulization [15].

The nebulizers were weighed (Sartorius 1216MP, Gottingen, Germany) before and after nebulization in order to calculate the amount of drug or placebo nebulized. A stopper was placed in the output hole during weighing to reduce loss of volume by evaporation. Initially 1 ml clemastine, taken from 2 mg·2 ml^{-1} solution, was added to 2 ml sterile water. The 3 ml of solution (final concentration of clemastine 0.3 mg·ml^{-1}) was then placed in the jet nebulizer and nebulized almost to completion. The estimated mean dose±SD of clemastine nebulized in approximately 3 min was 0.42±0.08 mg.

To facilitate quantitation of the drug delivered, 5 ml clemastine (0.3 mg·ml^{-1}) was nebulized for a set period of 5 min. The estimated mean±SD dose of clemastine nebulized in 5 min was 0.49±0.11 mg.

Statistical analysis

Lung function at rest. The mean values for baseline FEV_1, expressed as % predicted [16] measured pre-medication, were compared on active and placebo days (fig. 1). Comparisons were made, using paired t-tests, between pre-medication and post-medication values of FEV_1 (on both active and placebo days) to assess if a significant change in lung function occurred after the inhalation of clemastine, normal saline, or placebo.

Changes in response to non-isotonic aerosols. All values for FEV_1 measured after challenge on the active and placebo day were compared at the same concentration of histamine, hypertonic saline or hypotonic saline. Thus FEV_1 values were compared at the highest concentration of histamine or hypertonic saline and the lowest concentration of hypotonic saline delivered on both days. A paired t-test was used to test these comparisons and a p value less than 0.05 was regarded as significant.

To quantitate the airway response to bronchial challenge the percent fall index (% Fall) was used. This was measured as the reduction in FEV_1 after challenge expressed as a percentage of the pre-challenge post-medication value. These values were compared on the active drug and its placebo using a paired t-test. The percent fall index was used in preference to PC_{20} as many subjects did not record a 20% fall in FEV_1 in the presence of the active drug. It also has the advantage of taking into account changes in baseline FEV_1.

The severity of the response was also calculated by comparing the values for FEV_1, expressed as a percentage of the predicted normal, on the active and placebo days, before and after medication, and after challenge with the same concentration of saline. These comparisons were made using a paired t-test. This analysis serves as a useful clinical guide to severity.

To assess the protection afforded by clemastine against the bronchial challenges, the difference between the FEV_1 (expressed as a percentage of the predicted normal value) measured before the challenge but after medication, and the lowest FEV_1 measured after challenge was calculated on the active and placebo day. This analysis of differences in percent predicted was made because it also takes into account changes in baseline FEV_1 [3] (fig. 1).

The % protection was calculated by taking the difference between the values on the placebo and active days and expressing it as a percentage of the value observed on the placebo day (fig. 1). The % protection given by clemastine was calculated for each individual subject for both the 15 min and 90 min protocols. A value of 50% or more for % protection is taken as significant.

A Spearman's rank order correlation was used to compare the sensitivity of the subjects to hypertonic and hypotonic challenge, and the protection provided by clemastine.

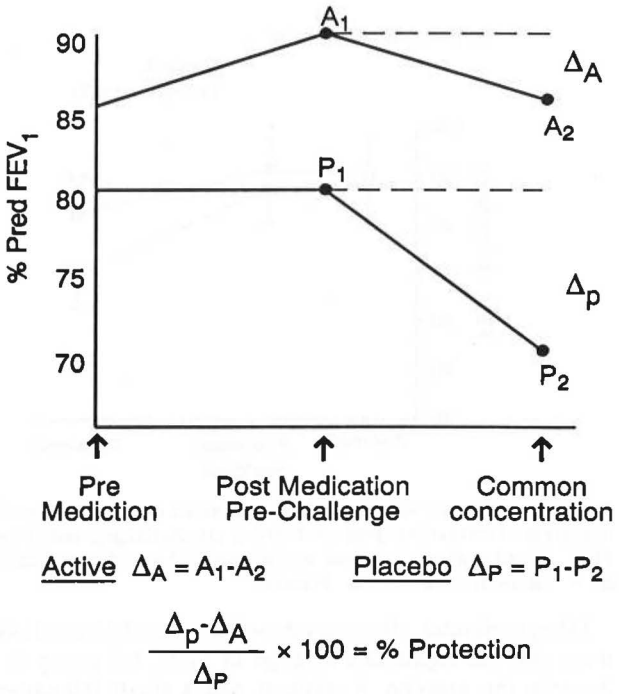

Fig. 1. – Calculation of protection afforded by clemastine, accounting for changes in baseline function induced by the drug. FEV_1: forced expiratory volume in one second.

Results

Lung function at rest

There was no significant difference in the pre-medication values for FEV_1 on the active and placebo days for any of the challenge days either in Group A or B (fig. 2). Similarly, there was no significant change in FEV_1 in Groups A and B after the inhalation of the placebo on the three test days it was given (table 2). However, some subjects had a small reduction in FEV_1. For Group A 5 out of 8 subjects recorded a reduction in FEV_1 after placebo on 10 of the 23 occasions it was given. The mean±SD fall in FEV_1 expressed as % predicted was 5.5±3.46 (range 0.3–10.6). For Group B, 6 out of 8 subjects recorded a fall on 9 out of 24 occasions and the mean was 3.1±2.74 (range 0.9–9.0).

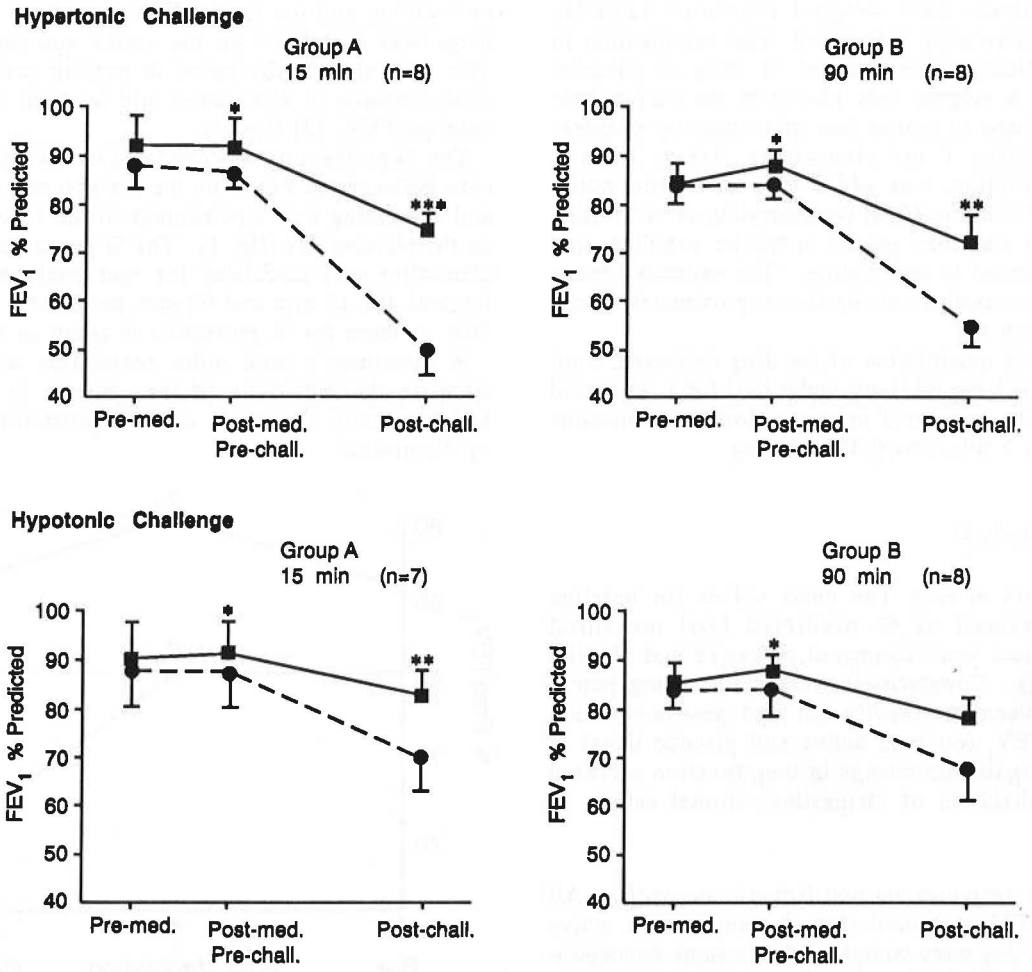

Fig. 2. – Mean±SD values for FEV_1, expressed as a percentage of the predicted value, before (pre-medication), and 15 or 90 min after the inhalation of clemastine (post-medication, pre-challenge); and at the highest and lowest concentration of saline common to the two test days. FEV_1: forced expiratory volume in one second; level of significance between active and placebo days - *: p<0.05; **: p<0.02; ***: p<0.005; ■——■ Active; ●- —-● Placebo.

Fifteen minutes after the administration of clemastine there was no significant change in FEV_1 for group A. As with the placebo, 4 subjects had a small reduction FEV_1 15 min after clemastine was given, mean 5.3±5.8 (range 0.3–13.1).

For Group B, however, there was a small but statistically significant improvement in FEV_1 90 min after the administration of clemastine (table 2).

When the values for FEV_1 were compared after the administration of clemastine and the placebo, the values were significantly higher in the presence of clemastine on most occasions (fig. 2). There was no significant difference in FEV_1 before and after the administration of 0.9% saline, mean±SD 83.4±11.0 before, and 83.1±10.3 after.

Change in FEV_1 in response to challenge. Clemastine significantly reduced the histamine-induced % Fall in FEV_1 both at 15 min (Group A) (p<0.003) and 90 min (Group B) (p<0.0005) (fig. 3) indicating that it was antagonising histamine receptors in the airways. The mean (geometric) dose of histamine required to induce the reduction in FEV_1 illustrated in figure 3 was 0.87 μmoles and the range was 0.04–6.37 μmoles.

Table 2. – Mean values (SD) for FEV_1, expressed as % predicted, before and after the administration of the placebo and the clemastine on the three test days

15 min - Group A

		Histamine	Hypertonic	Hypotonic
Placebo	Pre	87.9 (21.1)	89.2 (14.8)	88.7 (21.7)
		NS	NS	NS
	post	87.5 (15.0)	87.1 (11.7)	88.4 (19.8)
Clemastine	Pre	90.0 (16.2)	91.8 (18.1)	90.9 (16.2)
		NS	NS	NS
	Post	89.9 (3.8)	91.7 (19.5)	92.1 (16.4)

90 min - Group B

		Histamine	Hypertonic	Hypotonic
Placebo	Pre	80.9 (10.4)	83.8 (8.7)	85.1 (12.7)
		NS	NS	NS
	Post	80.3 (11.0)	85.2 (9.8)	84.2 (13.6)
Clemastine	Pre	79.5 (12.0)	84.8 (9.5)	85.8 (9.8)
		*	***	**
	Post	85.1 (8.0)	88.4 (10.0)	88.5 (15.7)

*: p<0.025; **p<0.01; *** p<0.005; NS: not significant; FEV_1; forced expiratory volume in one second.

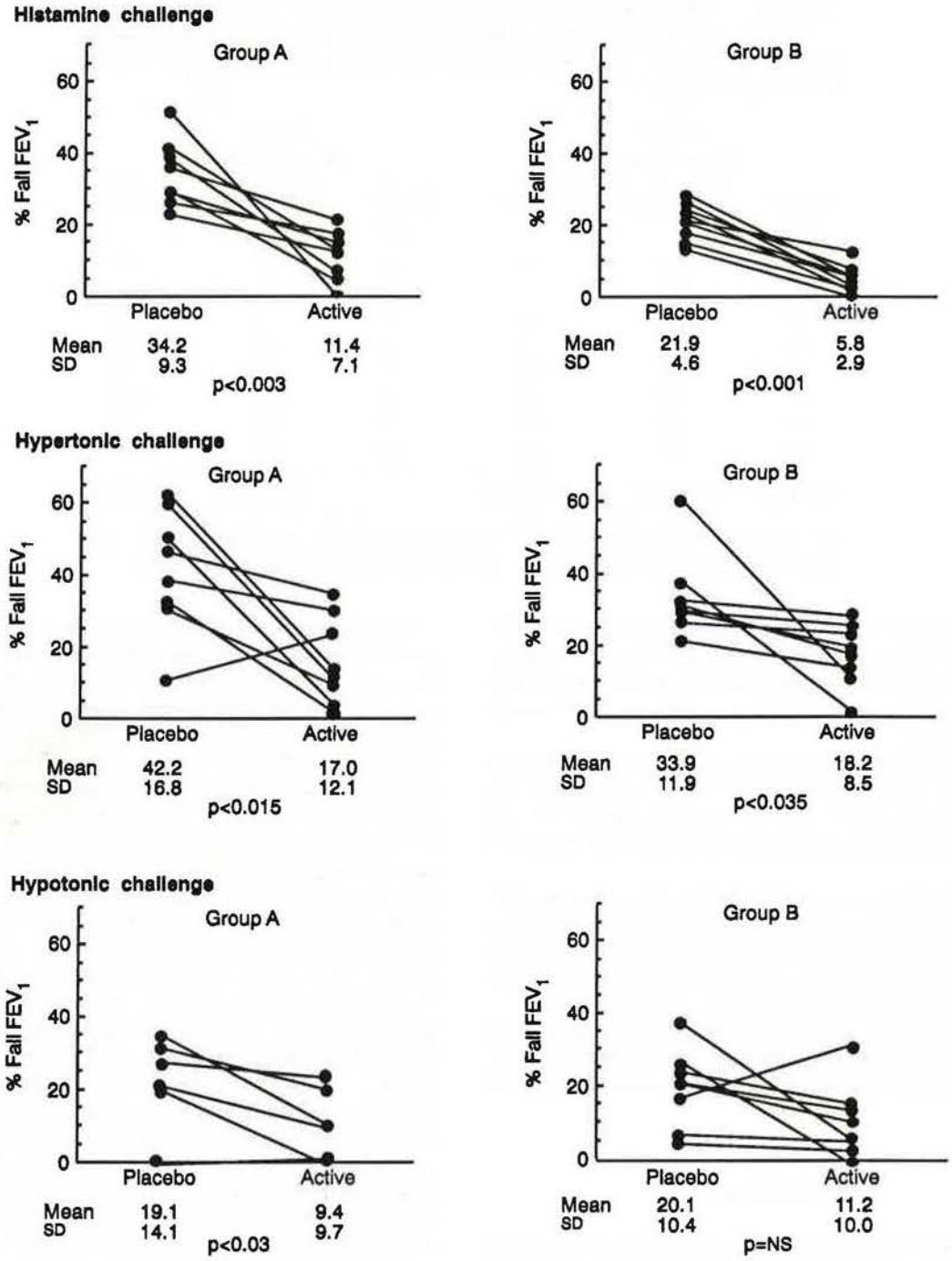

Fig. 3. – The maximum % fall in FEV_1 at the highest concentration common to both active and placebo days for hypertonic and histamine challenges, and the lowest concentration common to both active and placebo days for hypotonic challenge. FEV_1: forced expiratory volume in one second.

Clemastine significantly reduced the % Fall in FEV_1 on both hypertonic and hypotonic challenge at 15 min (Group A) and on the hypertonic challenge at 90 min (Group B) (fig. 3).

The values for FEV_1, expressed as a percentage of the predicted normal, after challenge with hypertonic aerosols were significantly higher both 15 min (Group A) and 90 min (Group B) after clemastine (fig. 2). After hypotonic aerosol challenge the values for FEV_1 were significantly higher only at 15 min.

The % protection afforded by clemastine against the hypertonic challenges was better at 15 min (Group A) than at 90 min (Group B). Five out of 8 subjects had a greater than 50% protection when clemastine was inhaled 15 min before hypertonic challenge, whereas only 2 out of 8 subjects had a greater than 50% protection at 90 min (table 3). For the hypotonic challenge, of the 10 who responded with a 20% fall 15 min and 90 min after placebo (fig. 3), only 5 had greater than 50% protection.

Table 3. – The % protection afforded by clemastine when inhaled either; 1. 15 min; or 2. 90 min before a progressive hypertonic or hypotonic saline aerosol challenge. The % protection was calculated as $\frac{\Delta_P-\Delta_A}{\Delta_P} \times 100$ as illustrated in figure 1

15 min % protection			90 min % protection		
Subject no.	Hypertonic	Hypotonic	Subject no.	Hypertonic	Hypotonic
6	89	32	1	10	79
8	12	17	2	40	NR
9	93	NR	3	1	40
10	0	-	4	14	30
11	67	51	5	31	33
13	80	NR	6	80	100
14	16	66	7	33	0
15	78	100	10	93	NR
Mean±SD	54.3±38.2	53.1±28.9		37.9±32.9	47.1±33.1

NR: Subjects who did not respond with a greater than 20% fall in FEV_1 after hypotonic saline challenge; FEV_1: forced expiratory volume in one second.

There was no relationship between changes in FEV_1 induced by clemastine at rest and the protective effect afforded by the drug against challenge either at 15 min ($r=0.15$, $n=21$, p=NS) or at 90 min ($r=0.13$, $n=31$, p=NS) after the drug.

Only two subjects, Numbers 6 and 10, were common to Groups A and B. Subject 6 was protected by clemastine both at 15 and 90 min but Subject No 10 was not protected by clemastine at 15 min but was at 90 min.

When the % protection afforded by clemastine against the three challenge tests were compared there was a significant relationship between the protection against challenge with histamine and hypertonic saline for the 15 min study (Group A) ($r_s=0.74$, $p<0.05$, $n=8$).

Subjects did not complain of any adverse side-effects related to the administration of clemastine and they all tolerated the inhalation of the non-isotonic aerosols well.

Discussion

This study demonstrates that clemastine, a histamine H_1-receptor antagonist administered as an inhaled aerosol, had a significant protective effect against airway narrowing caused by the inhalation of non-isotonic aerosols. The protective effect was more evident against challenge with hypertonic saline particularly 15 min after administration of the drug. Clemastine was also effective against challenge with hypotonic aerosol in some subjects.

These findings confirm the suggestion that histamine is an important mediator in the airway narrowing provoked by an increase in airway osmolarity and provides indirect evidence that mast cell degranulation occurs in response to the inhalation of aerosols of hypertonic saline.

Initially we chose 90 min as the interval between the dose of clemastine and the challenge. This interval was based on the study by HARTLEY and NOGRADY [11] which demonstrated the effectiveness of clemastine at this dose in exercise-induced asthma. The findings in the 90 min study (Group B) were not as clear as we would have predicted based on our earlier findings with terfenadine administered orally [3]. Only 2 subjects had more than 50% protection afforded by clemastine aerosol against the challenge with hypertonic and hypotonic aerosols. For this reason we repeated the study using the same dose of clemastine but reduced the time interval between drug and challenge to 15 min. For this study (Group A) 5 of the 8 subjects had protection afforded by clemastine and for this sub-group the mean±SD protection was 81±10%, suggesting that in these subjects histamine was the primary mediator of the airway response to hypertonic challenge. Unfortunately we did not increase the dose of clemastine in the other subjects to ascertain whether failure to block was merely due to a sub-optimal concentration of drug being delivered to the airways. This response could also have been due to the action of other mediators released from mast cells. Although it is likely that other mediators are involved in the airway response to hyperosmolar saline, evidence from the studies *in vivo* [6,17] and *in vitro* suggests that neither prostaglandins nor leukotrienes are released in response to this stimulus [18].

It was important to establish that the protective effect of clemastine was not due solely to its bronchodilating action. Both the % fall in FEV_1 and the protection afforded by clemastine were calculated from the value for FEV_1 measured after clemastine and immediately before the bronchial challenge. This method of analysis took into account the changes in baseline FEV_1 following inhalation of the active drug or placebo. The protective effect afforded by clemastine was not explained by changes in FEV_1 induced by the drug. In

Group A there was no significant change in FEV_1 15 min after clemastine but excellent protection occurred in most subjects. In Group B, who were challenged 90 min after clemastine inhalation, there was an increase in FEV_1 from lung function at rest. However, this was not related to the protection provided by clemastine.

There are conflicting data concerning the bronchodilating effects of clemastine. In contrast to our study, NOGRADY *et al.* [19], reported a 13% increase in FEV_1 15 min after inhalation of clemastine, with a 21% increase at 90 min in hospitalized patients recovering from exacerbations of asthma. Other investigators report no bronchodilatation occurring in groups of clinically stable asthmatics after inhaling 0.5 mg clemastine in either 1 ml or 2 ml of solution [20, 21]. These variations may be explained by differences in the concentration of background histamine and its effect on resting airway tone. Another explanation may be that the subjects in the 15 min study had relatively good lung function so there was less room for improvement compared with the subjects studied at 90 min. We think it unlikely that the improvement in FEV_1 90 min after clemastine results from any anti-cholinergic activity as clemastine does not attenuate airway narrowing provoked by methacholine [9].

The osmolality of clemastine and placebo was high even though they were diluted with sterile water. The high osmolality is the likely reason that some subjects had small falls from baseline FEV_1 15 min after inhaling clemastine or the placebo. This was not evident at 90 min probably because the small changes in FEV_1 had reversed and the clemastine had time to exert its effect as a bronchodilator. Other investigators have not reported any reduction in lung function in response to inhaling aerosols of clemastine or its placebo [9, 22, 23].

We studied two groups of asthmatic subjects and only two subjects were in both groups. However, subjects in both groups had 20% fall in FEV_1 to inhaled hypertonic saline and, in addition, all had some protection against this challenge after clemastine. This suggests that hypertonic saline caused airway narrowing by a similar mechanism in both groups. Subjects were less sensitive to the hypotonic challenge than the hypertonic challenge. Subjects Nos. 9 and 13 (15 min protocol) and Nos. 2 and 10 (90 min protocol) did not respond to the hypotonic challenge on placebo day. This difference in response, within the same subject, to hypotonic and hypertonic aerosols has also been observed by other investigators [3, 24]. The reason for the difference is unknown but it may relate to differences in the site of deposition of the hypotonic and hypertonic aerosols in the airways, the nature and amount of mediators released in response to an increase or a decrease in osmolarity, or to the technique used to challenge with hypotonic aerosols. In this study distilled water (the usual hypotonic stimulus) was not used, so the reduction in osmolarity probably occurred more slowly than it would have if distilled water had been used throughout the challenge. The progressive hypotonic challenge may not be as sensitive because under conditions of gradual change there may be adaptation.

Higher concentrations of antihistamine are likely to be achieved in the airways by using the inhaled route of administration. Furthermore, this route of administration is not associated with the same side-effects of drowsiness as when the same drug is given orally. We were uncertain of the potency of terfenadine compared with clemastine under these study conditions. However, the protection provided by 0.5 mg of inhaled clemastine against challenge with non-isotonic aerosol compared favourably to the protection provided by 180 mg of terfenadine in an earlier study [3]. We chose 0.5 mg of clemastine because it had been shown to inhibit exercise-induced asthma. We would like to have increased the dose in order to determine if those subjects who did not block would have done so at a higher dose. Because the clemastine solution caused a small reduction in FEV_1 in some patients we consider that it is important to find an alternative method for delivering clemastine to the airway before investigating the effect of higher doses. Some of these problems could be overcome if clemastine could be administered as a powder from a spinhaler device.

The benefit from antihistamines, over treatment with beta-adrenoceptor agonists, may be in allowing rather than preventing the release of mediators from mast cells. The bronchoconstricting effects of histamine and other mediators may be blocked at specific receptors while the beneficial effects of other products which are released, particularly those contributing to the development of the refractory period, will not be lost.

In conclusion, histamine plays a role in the airway narrowing caused by inhaling non-isotonic aerosols in clinically well-controlled asthmatic subjects. This is demonstrated by the protective effect that inhaled clemastine had against these challenges. Clemastine, however, did not completely inhibit the airway narrowing induced by these aerosols, suggesting that mediators other than histamine are involved. Alternatively, the dose of clemastine was insufficient to abolish the effects of histamine at all H_1-receptors. Further studies are required to assess whether greater protection would be provided by increasing the dose of clemastine.

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L'inhalation de clemastine, un antihistaminique H_1, inhibe le rétrécissement des voies aériennes causé par des aérosols de solution saline non isotonique. L.T. Rodwell, S.D. Anderson, J.P. Seale.

Des sujets asthmatiques ont fait l'objet d'une provocation au moyen d'aérosols d'une solution saline hyper- et hypotonique, respectivement 15 minutes (Groupe A) et 90 minutes (Groupe B) après inhalation de clemastine. Le VEMS a été mesuré avant après médication, et après provocation. Lorsque les valeurs du VEMS (en % des valeurs prédites) sont comparées les jours avec traitement actif par rapport aux jours placebo, elles s'avèrent plus élevées 15 minutes après la clemastine ($p<0.05$) pour les deux provocations, et également plus élevées 90 minutes après inhalation de clemastine ($p<0.05$) en cas de provocation hypertonique. Le pourcentage de chute du VEMS a été comparé après que la même concentration de solution saline en aérosol ait été administrée respectivement le jour traitment actif et du traitement placebo. Dans le Groupe A, le pourcentage de chute du VEMS le jour de la clemastine était réduit après provocation au moyen d'aérosol hypertonique ($p<0.02$) et hypotonique ($p<0.03$). Dans le Groupe B, l'on n'a observé de reduction du pourcentage de chute du VEMS le jour de la clemastine qu'après provocation hypertonique ($p<0.04$). L'effet protecteur obtenu par la clemastine est sans relation avec les modifications de l'état fonctionnel pulmonaire de base. Nous concluons que l'histamine est un médiateur important de la réponse des voies aériennes à des aérosols non isotoniques, et suggérons que la voie d'administration par aérosol pourrait être utile pour donner des antihistimaniques.

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