Role of histamine release in hypertonic saline induced bronchoconstriction

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ABSTRACT In a study designed to determine the protective effect of the specific histamine H_1 antagonist terfenadine on hypertonic saline induced bronchoconstriction, 10 asthmatic subjects underwent hypertonic saline challenge (3.6%) after premedication with placebo or terfenadine (120 mg) 12 and two hours before the challenge. Hypertonic saline was administered in a dose dependent manner and the response determined as the dose of hypertonic saline that induced a 20% fall in FEV_1 ($PD_{20} FEV_1$). FEV_1 was on average 11% greater with terfenadine than with placebo given before the challenge with hypertonic saline. $PD_{20} FEV_1$ was attenuated by a mean of 2.5 fold after terfenadine (geometric mean $PD_{20} FEV_1$ was 22 litres after placebo and 56 l after terfenadine). There was substantial intersubject variation in the inhibitory effect of terfenadine on hypertonic saline induced bronchoconstriction: the ratio of the PD_{20} hypertonic saline after terfenadine to that after placebo ranged from 0.9 to 10.0. Terfenadine inhibited histamine induced bronchoconstriction in the eight subjects in whom it was tested, by 13 to 160 fold compared with placebo in four subjects and by > 2 to > 9 fold in the four who showed no response to the highest dose of histamine given (16 mg/ml). These results suggest that histamine release has a role in hypertonic saline induced bronchoconstriction in some individuals; other mediators or mechanisms may have a more prominent role in others.

Introduction

Inhalation of hypertonic saline elicits bronchoconstriction in many people with asthma.^{1,2} Airway responsiveness to aerosolised hypertonic saline has been shown to be correlated with responsiveness to inhaled methacholine,^{3,4} histamine,⁵ and exercise.⁶ In common with inhalation of ultrasonically nebulised distilled water⁷ and exercise induced asthma,⁸ the inhalation of hypertonic saline may be followed by the development of a refractory period during which a second, identical challenge will cause significantly less bronchoconstriction.⁹ Hypertonic saline induced bronchoconstriction is accompanied by the release of high molecular weight neutrophil chemotactic activity,¹⁰ suggesting that mast cell associated mediators may be released by the hyperosmolar stimulus to the bronchial mucosa. It is not, however, associated with an increase in venous plasma histamine concentrations,¹⁰ though histamine is released in vivo, as judged by measurements made

on bronchoalveolar lavage fluid.¹¹ It has been suggested that hypertonic saline inhalation may release histamine locally in the airways, but that the quantities produced are too small to be detected in the systemic circulation.¹⁰

We have assessed the role of histamine release in hypertonic saline induced bronchoconstriction by determining the effect of terfenadine, a potent and selective histamine H_1 receptor antagonist, on the airway responsiveness to hypertonic saline.

Methods

SUBJECTS

We studied 10 asthmatic subjects (seven male, three female) aged 19-47 (mean 25.5) years. Nine subjects were taking regular inhaled beclomethasone dipropionate (dose 200-1000 μ g daily), and all used inhaled beta₂ sympathomimetic agonists as required. Nine subjects were atopic as defined by positive skin test responses (a weal at least 3 mm larger than with the saline control solution) to a range of common aeroallergens (grass, dog, cat, *Dermatophagoides pteronyssinus*). No subject had taken oral corticosteroids for at least one month before challenge and no

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subject was taking other antiasthmatic drugs (including histamine antagonists).

STUDY DESIGN

Ten subjects underwent two hypertonic saline challenges separated by one week. Each challenge was preceded by the administration of either 120 mg terfenadine or matching placebo capsules in a double blind manner 12 and two hours before the hypertonic saline challenge. Eight of the 10 subjects also underwent two histamine challenges preceded by the administration of terfenadine or matching placebo, as described above. All other medication was withheld for 12 hours before each visit to the laboratory. All challenges for each subject were performed at the same time of day. The study was approved by the Guy's Hospital ethical committee and each subject gave informed consent.

HYPERTONIC SALINE CHALLENGE

Hypertonic saline challenges were performed with a Devilbiss 65 Ultrasonic nebuliser as previously described.⁹ The subject inhaled twofold increasing volumes of hypertonic (3.6%) saline, starting at 5 litres, until there was a greater than 20% fall in FEV₁ or until a maximum cumulative dose of 315 litres of hypertonic saline was reached. Measurements of FEV₁ were made in duplicate on a dry bellows spirometer (Vitalograph, Buckingham) at 30, 60, and 90 seconds after each dose of hypertonic saline and the highest reading was recorded. If the required decrease in FEV₁ was not reached the next dose of saline was given. The dose of hypertonic saline producing a 20% fall in FEV₁ (PD₂₀) was determined by linear interpolation of the last two points of the log dose-response curve.

HISTAMINE CHALLENGE

Histamine acid phosphate in isotonic buffered saline was delivered from a Wright nebuliser driven at a flow rate of 8 l/min at 20 lb/in² (138 kPa; output 0.14 ml/min). Histamine was inhaled during two minutes of tidal breathing. Doubling concentrations from 0.0625 mg/ml were used until a 20% fall in FEV₁ was achieved or a maximum concentration of 16.0 mg/ml was delivered. The FEV₁ was measured 0.5, one, and three minutes after inhalation of histamine and the concentration of histamine required to produce a 20% fall in FEV₁ (PC₂₀ histamine) was determined by linear interpolation from the last two points of the log dose-response curve.

DATA ANALYSIS

Differences in PD₂₀ hypertonic saline between placebo and terfenadine days were analysed by a paired *t* test of log transformed data. Correlations were assessed by linear regression analysis of the log transformed data.

Results

EFFECT OF TERFENADINE ON AIRWAY RESPONSE TO HYPERTONIC SALINE

The mean (SEM) FEV₁ was significantly less after administration of placebo (3.06 (0.19) l) than of terfenadine (3.38 (0.22) l; *p* = 0.009). The airway response to hypertonic saline was significantly attenuated by terfenadine (table 1). The geometric mean PD₂₀ hypertonic saline was 22 (range 3–235) litres after placebo and 56 (range 10–315) after terfenadine (*p* = 0.007, *n* = 10; table 1). There was a 10 fold variation between subjects in the change in PD₂₀ hypertonic saline after terfenadine premedication (table 1). The change in PD₂₀ hypertonic saline after terfenadine was not correlated with resting FEV₁ before hypertonic saline challenge on the terfenadine or placebo days (*r* = 0.2, *p* = 0.5), or with the subject's daily dose of inhaled beclomethasone dipropionate (*r* = -0.17, *p* = 0.6).

EFFECT OF TERFENADINE ON AIRWAY RESPONSE TO HISTAMINE

Two of the 10 subjects declined histamine challenge. In the other eight subjects terfenadine caused significant protection against histamine bronchoconstriction (*p* = 0.001), the ratio of PC₂₀ histamine following terfenadine to that following placebo ranging from >2.0 to 160 fold (table 2). Four of the five subjects in whom terfenadine caused minimal or no protection against hypertonic saline induced bronchoconstriction (subjects 2, 7, 8, and 9) underwent histamine challenge; all were protected against histamine induced bronchoconstriction.

Table 1 FEV₁ after placebo and terfenadine, the dose of hypertonic saline that produced a 20% fall in FEV₁ (PD₂₀) after placebo and terfenadine, and the ratio of PD₂₀ terfenadine to PD₂₀ placebo

Subject No	Placebo		Terfenadine		
	FEV ₁ (litres)	PD ₂₀ (litres)	FEV ₁ (litres)	PD ₂₀ (litres)	PD ₂₀ ratio
1	2.2	25	2.2	200	8.0
2	3.4	7	3.7	10	1.4
3	3.1	14	3.9	100	7.1
4	3.5	14	3.7	33	2.3
5	3.8	36	3.7	92	2.5
6	2.4	3	2.8	30	10.0
7	2.6	24	2.6	23	0.9
8	2.4	37	2.9	43	1.2
9	3.5	35	4.3	58	1.6
10	3.7	235	4.0	315	1.3
Mean*	3.06	22	3.38	56	2.5

*Arithmetic mean for FEV₁ and geometric mean for PD₂₀.

Table 2 FEV_1 after placebo and terfenadine, the concentration of histamine that produced a 20% fall in FEV_1 (PC_{20}) after placebo and after terfenadine, and the ratio of PC_{20} histamine after terfenadine to PC_{20} histamine after placebo

Subject No	Placebo		Terfenadine		PC_{20} ratio
	FEV_1 (litres)	PC_{20} (mg/ml)	FEV_1 (litres)	PC_{20} (mg/ml)	
2	3.6	8.00	3.9	> 16.0	> 2
3	2.7	2.30	3.8	> 16.0	> 6.9
4	2.7	1.80	2.2	> 16.0	> 8.9
5	3.5	2.30	3.8	> 16.0	> 6.9
6	2.4	0.13	2.5	12.0	92.3
7	2.1	0.58	2.4	8.0	13.8
8	3.4	1.00	2.7	16.0	16.0
9	3.5	0.05	3.8	8.0	160.0
Mean	3.0		3.1		

Discussion

Intrabronchial challenge of the airways with hypertonic saline in vivo results in the local release of histamine, suggesting that this mediator may contribute to bronchoconstriction.¹¹ This view is supported by the results of the present cumulative dose-response study, which showed a significant reduction in airway responsiveness to hypertonic saline after premedication with the potent and selective histamine H_1 receptor antagonist terfenadine. The dose of terfenadine given has been shown to attenuate the airway response to inhaled histamine.¹² Terfenadine induced a significant degree of bronchodilatation but this was not related to the change in airway responsiveness and there was no correlation between the degree of bronchodilatation and the magnitude of the decreases in responsiveness to hypertonic saline. As a drug that alters baseline airway calibre may influence the position of the dose-response curve of a bronchoconstrictor agonist, we have followed the principle of Chung *et al* and "normalised" the bronchoconstrictor dose-response curve to the postdrug baseline, thereby removing the influence of baseline airway calibre on the bronchoconstrictor response.¹³ Using this procedure, Rafferty and Holgate¹² and Patel¹⁴ have shown that although terfenadine causes bronchodilatation it does not alter airway responsiveness to inhaled methacholine, as determined by $PD_{20} FEV_1$. This indicates that bronchodilatation produced by terfenadine will not necessarily change PD_{20} .

Although the group as a whole had a significant reduction in airway responsiveness to hypertonic saline after terfenadine pretreatment, the protection afforded by terfenadine was variable. As terfenadine inhibited histamine induced bronchoconstriction in all

the subjects studied, the intersubject variability cannot be ascribed to a failure of terfenadine to inhibit the bronchoconstrictor action of histamine. The reason for the variable response is not known, but may reflect heterogeneity in the mechanisms responsible for hypertonic saline induced bronchoconstriction. It suggests that, although histamine release contributes to the pathogenesis of hypertonic saline induced asthma in some patients, other mediators or mechanisms may be important in other individuals.

There is continuing debate about the mechanism of exercise induced asthma.¹⁵ McFadden *et al* have suggested that respiratory heat loss¹⁶ is of major importance and that the rate of airway rewarming after exercise determines the degree of bronchoconstriction.¹⁷ Anderson and co-workers have suggested that change in bronchial mucosal osmolarity secondary to water loss during the hyperpnoea of exercise is the major factor in exercise induced asthma.¹⁸ In support of this, Ingenito and co-workers,¹⁹ using gases with similar water carrying capacities but significantly different volume-heat capacities, recently showed that total respiratory heat loss is not the primary stimulus in exercise induced asthma, and that water loss may be important in inducing bronchoconstriction in exercise induced asthma.

If hyperosmolarity is the cause of exercise induced asthma, the pharmacological modulation of hypertonic saline induced bronchoconstriction and exercise induced asthma should be identical. In support of this, our results with hypertonic saline induced bronchoconstriction are similar to those of Patel,²⁰ who found a small but significant protective effect of terfenadine on postexercise bronchoconstriction in 10 subjects, though in three no protection was seen after 60, 120, or 180 mg terfenadine administered three hours before exercise. Magnussen in a study of a single dose of azelastine (4.4 mg) showed significant attenuation of exercise induced asthma in 10 subjects, though three of these were not protected.²¹

In this study we have shown that the potent and selective histamine H_1 receptor antagonist terfenadine confers partial protection against hypertonic saline induced bronchoconstriction in some subjects. These results suggest that histamine release has a role in the bronchoconstriction induced by this challenge, but the pathogenetic mechanisms of hyperosmolar challenge may be heterogeneous.

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