

Loratadine reduces allergen-induced mucosal output of α_2 -macroglobulin and tryptase in allergic rhinitis

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Background: Despite the wide use of antihistamines in the treatment of allergic rhinitis, little is known about effects of these drugs on airway mucosal indices, which specifically reflect either mast cell release activity (tryptase) or microvascular-epithelial exudation of bulk plasma (α_2 -macroglobulin).

Objective: This study, involving subjects with seasonal allergic rhinitis, examines the effects of loratadine treatment on allergen-induced nasal mucosal output of tryptase and α_2 -macroglobulin. Effects on nasal symptoms and eosinophils are also examined.

Methods: Placebo and loratadine (20 mg) were given orally once daily for 5 days at 6-week intervals. Nasal diluent and allergen challenges were carried out on day 5. The mucosa was lavaged with saline solution after each challenge, and nasal lavage fluid levels of tryptase and α_2 -macroglobulin were determined. Nasal symptoms were scored, and nasal peak expiratory flow rates were measured. Superficial cells (eosinophils) were obtained with a brush device before and 24 hours after the allergen challenges.

Results: Allergen dose-dependently increased the nasal symptoms and the lavage fluid levels of α_2 -macroglobulin and tryptase. Allergen also reduced the nasal peak expiratory flow rates. Loratadine inhibited the exudation of α_2 -macroglobulin and reduced tryptase levels, nasal symptoms, and obstruction, but did not affect the number of eosinophils.

Conclusion: The inhibitory effects of loratadine on nasal lavage fluid levels of α_2 -macroglobulin suggest that histamine, through effects on microvascular H_1 -receptors, mediates allergen challenge-induced exudation of bulk plasma in acute allergic rhinitis. The reduced lavage fluid levels of tryptase suggest either that loratadine directly attenuates mast cell release activity or that loratadine, through inhibition of the exudation process, simply attenuates luminal entry of tissue solutes (in this case, tryptase). (*J ALLERGY CLIN IMMUNOL* 1995;96:97-103.)

Key words: Airway, allergy, antihistamine, epithelium, human, inflammation, mast cell, microcirculation, permeability, plasma exudation

Antihistamines have been used in the treatment of allergic airway disease for more than 40 years. Their effects are ascribed to specific pharmacologic

Abbreviation used

SQ-U: Standardized quantity unit

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Supported by Swedish Medical Research Council (Project 8308), Medical Faculty of Lund University, and Swedish Association against Asthma and Allergy.

Received for publication Aug. 5, 1994; revised Dec. 6, 1994; accepted for publication Dec. 6, 1994.

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0091-6749/95 \$3.00 + 0 1/1/62582

antagonism of H_1 histamine receptors in different end organs of the airway mucosa.¹ The antihistamines may also produce other effects of potential therapeutic interest. For example, the observation that terfenadine and loratadine decrease allergen challenge-induced mucosal output of histamine in allergic rhinitis²⁻⁴ has been treated as evidence for a mast cell-stabilizing effect of antihistamines. However, a study involving cetirizine could not demonstrate this effect.⁵ Histamine is responsible

TABLE I. Nasal symptoms in response to diluent and allergen challenges after placebo and loratadine treatment

Challenge	Sneezes							Secretion						
	Placebo percentiles			Loratadine percentiles			<i>p</i> Value	Placebo percentiles			Loratadine percentiles			<i>p</i> Value
	25th	50th	75th	25th	50th	75th		25th	50th	75th	25th	50th	75th	
Before challenge	0	0	0	0	0	0	NS	0	0	1	0	0	0	NS
Diluent	0	0	0	0	0	0	NS	0	0	0, 5	0	0	0, 5	NS
Allergen 10 ² SQ-U	3	4	4, 5	0	0	0	<0.05	1	2	2, 5	0	0, 5	1	<0.05
Allergen 10 ³ SQ-U	0, 5	5	5, 5	0	0	0	<0.01	1	2	2, 5	0	1	1	<0.05
Allergen 10 ⁴ SQ-U	2	3.5	2, 5	0	0	0, 5	<0.05	1, 5	2, 5	3	0, 5	1	2	<0.05

NS, Nonsignificant.

for many pharmacologic effects induced by mast cell activation but may not be a specific marker of mast cell degranulation. Histamine may also be released by basophils,⁶ and histamine is normally present in nasal mucosal surface liquids in rather high and variable concentrations.⁷ In contrast to histamine, tryptase appears to be a specific mast cell mediator.⁷⁻¹⁰ Lavage fluid concentrations of tryptase may thus provide a useful surface index of mast cell degranulation in allergic airway disease.⁷

Increased permeability of the subepithelial microcirculation, extravasation, and luminal entry of bulk plasma (mucosal exudation) are key features of histamine-induced and allergen challenge-induced airway responses.¹¹ It has previously been demonstrated that terfenadine reduces allergen-induced nasal mucosal output of albumin.³ Because histamine is a potent inducer of plasma exudation in the nasal airway,¹² it is likely that the albumin measured in the terfenadine study reflects plasma exudation. However, albumin is a relatively small protein, and its presence in airway mucosal surface liquids may reflect several processes including passive diffusion, secretion, and mucosal exudation of plasma. The extravasation and epithelial passage of plasma involves little size restriction.¹¹ Particularly in experiments with bronchoalveolar lavage, we have observed that larger proteins, such as fibrinogen¹³ and α_2 -macroglobulin,¹⁴ are better markers of the plasma exudation response than albumin.

In this study, involving subjects with seasonal allergic rhinitis, we have continued the examination of effects of antihistamines on the allergen-challenged nasal mucosa. The selected treatment,

loratadine 20 mg, was given orally for 5 days. Nasal lavage fluid levels of tryptase and α_2 -macroglobulin (725 kd) were determined as indices of mast cell degranulation and mucosal exudation of plasma, respectively. Furthermore, the effects of loratadine treatment on allergen challenge-induced nasal symptoms and eosinophilia were examined.

METHODS

Study design and subjects

Subjects with timothy pollen-induced allergic rhinitis were studied in a randomized, double-blind, placebo-controlled, crossover trial. After oral treatment with loratadine and placebo, respectively, once daily for 5 days, nasal allergen challenges were carried out on treatment day 5. There was then a washout period of 6 weeks between the first and second treatment periods. The study was performed out of the timothy pollen season.

Ten men (aged 18 to 36 years) and two women (aged 24 years) participated in the study. The patients had a history of strictly timothy pollen-induced allergic rhinitis, which was verified by a positive skin prick test response to timothy allergen (Aquagen SQ; ALK, Gothenburg, Sweden). The study was performed according to the Helsinki Declaration after approval by the local ethics committee was obtained. Informed consent was obtained from the subjects.

Study drug

Loratadine (20 mg) or placebo was given orally once daily for 5 days. The subjects were provided with an allocation number, and the order of treatment proceeded according to a randomization scheme of the allocation numbers. Identical appearance and taste of the study drug and the placebo preparation assured that subjects did not know which they were receiving.

Blockage						
Placebo percentiles			Loratadine percentiles			p Value
25th	50th	75th	25th	50th	75th	
0	0	1	0	0	1	NS
0	0	0	1	0	1	NS
1	1	1, 5	0	0	1	NS
1	2	2	0	1	1, 5	<0.05
2	2	3	0	1, 5	2	<0.05

Allergen challenge and isotonic saline lavage

The challenges and lavages were carried out about 2 hours after placebo and loratadine administration, respectively, on treatment day 5. Seven nasal isotonic saline lavages were thus carried out at 10 minute intervals with a head-back lavage technique.¹⁵ The first three lavages were performed to remove solutes that might have accumulated on the mucosal surface and to establish a baseline value. The first and second of these lavages were thus not collected. Diluent and allergen (10^2 , 10^3 , and 10^4 SQ-U) in diluent (Aquagen SQ; ALK, Gothenburg, Sweden) were administered as single actuations (100 μ l) with a pump spray device. The challenges were performed about 1 minute after the preceding lavage, starting after the third lavage, and thus about 9 minutes before the subsequent lavage. The challenges were carried out in the right nasal cavity, whereas the lavages (2×5 ml) were carried out in both nasal cavities. The recovered lavage fluids were centrifuged (105 g for 8 minutes), and aliquots were prepared from the supernatants and frozen (-20° C) for later analysis of tryptase and α_2 -macroglobulin. Oxymetazoline (100 μ g) was administered as 2 actuations (100 μ l) with a pump spray device about 9 minutes before the third lavage to prevent allergen-induced nasal blockage. It has previously been demonstrated that this dose of oxymetazoline does not affect the mucosal output of either inflammatory mediators or various-sized plasma proteins induced by inflammatory challenges.^{12, 15}

Nasal symptom score and nasal peak expiratory flow measurement

Nasal symptoms (blockage and secretion) were scored by the subjects on scale from 0 to 3 before each lavage, and the number of sneezes was noted after each challenge. Nasal peak expiratory flow rates were measured immediately after each lavage with a nasal peak expiratory flow meter (Mini-Wright; Clement-Clarke, Harlow, U.K.).

Cell sampling

Cell specimens were obtained before and 24 hours after the allergen challenge series with a brush device (Interdental-brush; Apoteksbolaget, Gothenburg, Sweden).¹⁶ The brush was introduced into the left nasal cavity under visual control and placed between the nasal septa and the inferior turbinate. The brush was rotated 360 degrees and then removed. It was then placed in a tube and rinsed in 2 ml of isotonic saline solution. Cells were thus suspended, and 200 μ l of this suspension was loaded on a cytocentrifuge (Cytospin 2; Shandon, Pittsburgh, Pa.) and rotated (17 g for 8 minutes) onto glass slides, which were left to dry. The slides were stained according to the May-Grünwald-Giemsa method. A differential cell count was carried out by a single investigator, and only cells with well-preserved structure were counted.

α_2 -Macroglobulin measurement

The lavage fluid levels of α_2 -macroglobulin were measured with a radioimmunoassay sensitive to 7.8 ng/ml. Rabbit anti-human α_2 -macroglobulin (Dakopatts, Copenhagen, Denmark) was used as anti-serum, and standard human serum (Behringwerke Diagnostica, Marburg, Germany) was used as standard. Human α_2 -macroglobulin (Cappel-Organon Teknika, Turnhout, Belgium) was iodinated with the lactoperoxidase method. Tracer and standard (or sample) were mixed with anti-serum before goat anti-rabbit anti-serum (Astra Draco, Lund, Sweden) was added. The bound fraction was measured with a gamma counter (Pharmacia, Diagnostics, Uppsala, Sweden). The intra- and interassay coefficients of variation were between 3.8% to 6.0% and 3.1% to 7.2%, respectively.

Tryptase measurement

The lavage fluid levels of tryptase were analyzed with a modified radioimmunoassay sensitive to less than 0.5 ng/ml (Pharmacia Diagnostics, Uppsala, Sweden).¹⁷ Lavage fluid, sample diluent, and iodine 125-labeled anti-tryptase antibodies were simultaneously added to plastic tubes coated with anti-tryptase antibodies. After incubation for 16 to 18 hours, the tubes were washed three times and then counted in a gamma counter. The intra- and interassay coefficients of variation were both less than 3%.

Statistics

The Friedman test was used to examine differences in nasal symptoms, nasal peak expiratory flow rates, and lavage fluid concentrations of tryptase and α_2 -macroglobulin in subjects receiving placebo and loratadine treatment, respectively. If statistically significant differences emerged, the Wilcoxon signed-rank test was used for further analysis. The Wilcoxon signed-rank test was also used to compare symptoms, nasal peak expiratory flows, eosinophil numbers, and lavage fluid concentrations of tryptase and α_2 -macroglobulin, respectively, between subjects receiving placebo and loratadine treatment. A *p* value of less than 0.05 was considered significant. Data are presented as medians with 25th and 75th percentiles.

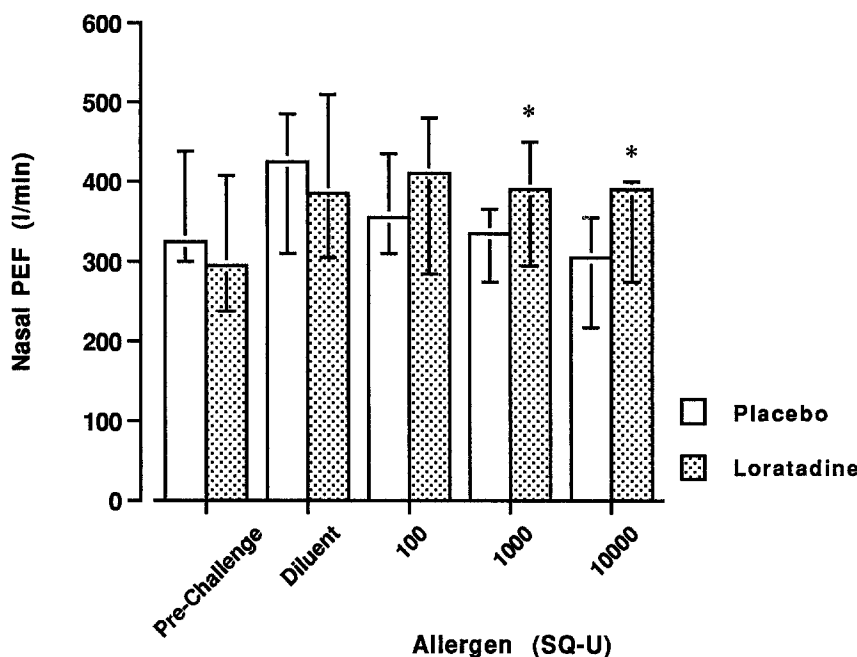


FIG. 1. Nasal peak expiratory flow rates in response to diluent and allergen challenges (10^2 , 10^3 , and 10^4 SQ-U) after placebo and loratadine treatment, respectively. Loratadine increased the nasal peak expiratory flow rates as compared with placebo. * $p < 0.05$. PEF, Peak expiratory flow.

RESULTS

Allergen produced dose-dependent increases in nasal symptoms in subjects receiving placebo treatment (Friedman test; $p < 0.0001$, all symptoms) (Table I). These increases were significant for the number of sneezes (all challenges; $p < 0.01$), for nasal secretion (all challenges; $p < 0.01$), and for nasal blockage (all challenges; $p < 0.01$) compared with diluent. Furthermore, allergen produced dose-dependent reductions in nasal peak expiratory flow rates (Friedman test; $p < 0.0001$, Wilcoxon test; $p < 0.01$, all challenges) compared with diluent (Fig. 1).

In subjects receiving loratadine treatment, nasal symptoms were suppressed (Table I). This effect was statistically significant for the number of sneezes ($p < 0.05$ to 0.01), for nasal secretion ($p < 0.05$), and for nasal blockage ($p < 0.05$) compared with placebo treatment. Furthermore, loratadine improved the nasal expiratory peak flow rates ($p < 0.05$) (Fig. 1). There were no statistical differences in nasal symptoms or in nasal peak expiratory flow rates between subjects receiving placebo and those receiving loratadine treatment after the diluent administrations.

Allergen produced dose-dependent increases in lavage fluid concentrations of tryptase in subjects receiving placebo treatment (Friedman test; $p < 0.0001$) (Fig. 2). These increases were significant for all allergen challenges ($p < 0.01$) compared

with diluent. In subjects receiving loratadine treatment, lavage fluid concentrations of tryptase were reduced (Fig. 2). This effect was statistically significant for allergen 10^2 SQ-U ($p < 0.01$), 10^3 SQ-U ($p < 0.05$), but not for allergen 10^4 SQ-U ($p = 0.07$) compared with placebo. There were no statistical differences in lavage fluid concentrations of tryptase after the diluent administrations.

Allergen produced dose-dependent increases in lavage fluid concentrations of α_2 -macroglobulin in subjects receiving placebo treatment (Friedman test; $p < 0.0001$) (Fig. 3). These increases were significant for all allergen challenges ($p < 0.01$) compared with diluent. In subjects receiving loratadine treatment, lavage fluid concentrations of α_2 -macroglobulin were much reduced (Fig. 3). This effect was statistically significant for allergen 10^2 and 10^3 SQ-U ($p < 0.01$) and 10^4 SQ-U ($p < 0.05$) compared with placebo. In subjects receiving loratadine treatment, only the highest dose of allergen (10^4 SQ-U) produced significant mucosal output of α_2 -macroglobulin (Friedman test; $p < 0.05$, Wilcoxon test; $p < 0.01$). There were no statistical differences in lavage fluid concentrations of α_2 -macroglobulin after the diluent administrations.

Allergen challenge produced influx of eosinophils in subjects receiving placebo, as well as in those receiving loratadine treatment ($p < 0.05$, both treatments). There was no significant difference between placebo and loratadine treatment in

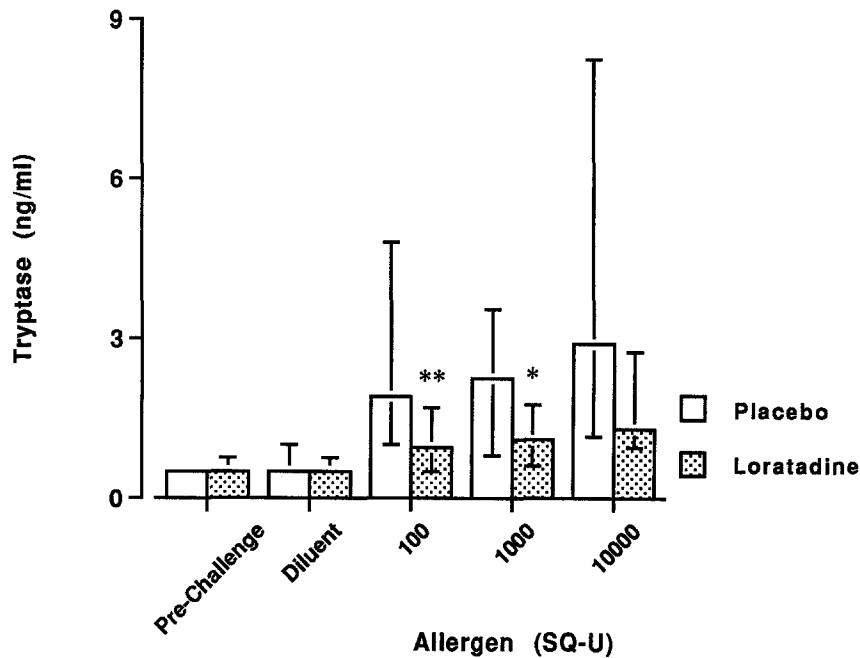


FIG. 2. Lavage fluid levels of tryptase in response to diluent and allergen challenges (10^2 , 10^3 , and 10^4 SQ-U) after placebo and loratadine treatment, respectively. Loratadine reduced the allergen-induced mucosal output of tryptase compared with placebo, suggesting reduced mast cell degranulation. * $p < 0.05$; ** $p < 0.01$.

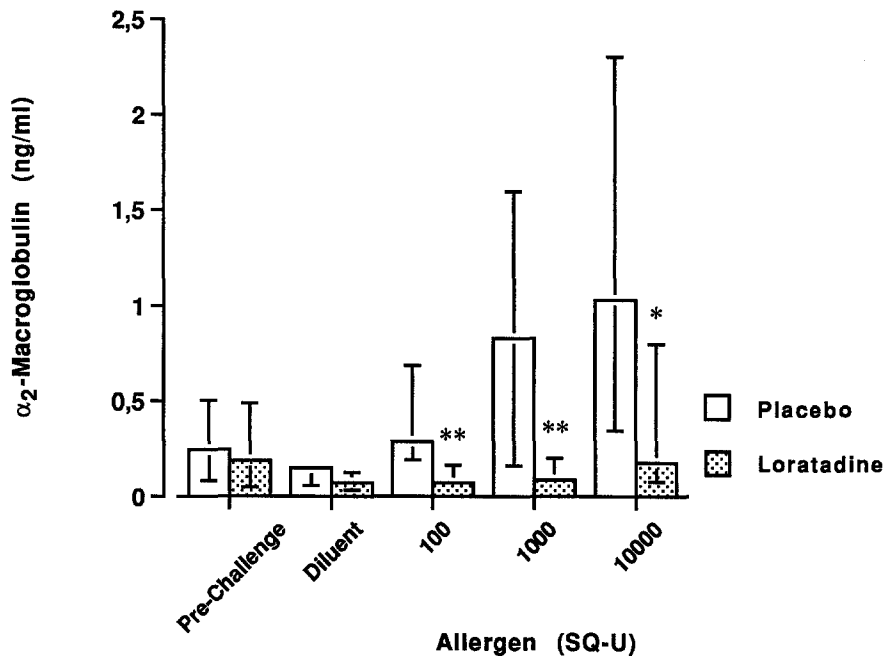


FIG. 3. Lavage fluid levels of α_2 -macroglobulin in response to diluent and allergen challenges (10^2 , 10^3 , and 10^4 SQ-U) after placebo and loratadine treatment, respectively. Loratadine reduced the allergen-induced mucosal output of α_2 -macroglobulin compared with placebo, indicating a decreased plasma exudation response. * $p < 0.05$; ** $p < 0.01$.

the eosinophil percentage recorded 24 hours after allergen challenge ($p = 0.5$). The percentage of eosinophils was 0% before the allergen challenges in both treatment groups and 4.0% (25th percen-

tile 0.3%, 75th percentile 10.7%) and 2.0% (25th percentile 0%, 75th percentile 9.5%), respectively, in the placebo and loratadine groups, 24 hours after allergen challenge.

DISCUSSION

This study, involving subjects with seasonal allergic rhinitis, has demonstrated that loratadine treatment reduces the allergen-induced nasal mucosal output of α_2 -macroglobulin and tryptase. Furthermore, it has demonstrated that loratadine suppresses the symptoms of allergic rhinitis, including nasal blockage, whereas allergen challenge-induced nasal eosinophilia is unaffected.

In this study allergen dose-dependently increased the mucosal output of α_2 -macroglobulin, and loratadine almost completely inhibited this response. The findings extend the previous observation on antihistamine-induced attenuation of albumin output³ and demonstrate that loratadine may inhibit the appearance of bulk plasma exudates on the allergen-challenged allergic airway mucosa. We have previously demonstrated that histamine challenges produce prompt exudation of albumin, fibrinogen, and α_2 -macroglobulin,¹⁸ and it is likely that loratadine inhibits the allergen-induced exudation by antagonizing the effect of acutely released histamine at H_1 -receptors located on the permeability-regulating endothelial cells of the subepithelial microcirculation. An effect on the permeability of the epithelial lining is not likely because the movement of bulk plasma through paracellular epithelial pathways appears to be a self-sustained process that is regulated by an increased hydrostatic pressure created by the exudate itself.^{19, 20} Mucosal exudation of bulk plasma may reflect the intensity and time course of epithelial-subepithelial inflammatory processes in the airways in allergy, occupational disease, infection, and other conditions.¹¹ However, it is doubtful whether the acute exudative effect of a single mediator, such as histamine, may be equated with inflammation. Similarly, a drug that reduces airway exudation of plasma through simple antagonism of such a single mediator may not be characterized as an antiinflammatory drug. In this study loratadine inhibited exudation of α_2 -macroglobulin more than it reduced the mucosal output of tryptase, suggesting that its main action was histamine antagonism.

It has previously been demonstrated that mucosal mast cells contain tryptase.⁸⁻¹⁰ Indeed, substantial amounts of tryptase (about 5 to 35 pg/cell, depending on mast cell subtype) have been found only in mast cells.^{9, 10} Tryptase is released together with other mast cell mediators,⁹ and it appears to be a specific marker of mast cell degranulation. Increased concentrations of tryptase in nasal mucosal surface liquids have previously been demonstrated in acute allergen-induced rhinitis.⁷ In the subjects in this study, the allergen-induced increase

in mucosal output of tryptase suggests that the mast cells responded well to the consecutive allergen challenges. In addition, this study demonstrates, for the first time, that antihistamine treatment reduces nasal mucosal output of tryptase, suggesting that loratadine specifically decreases mast cell degranulation. Whether loratadine also reduces mucosal surface levels of tryptase in sustained airway inflammation (e.g., during natural seasonal allergen exposure) remains to be examined. Any mast cell-stabilizing action of loratadine in this study would likely have contributed to the pronounced antiexudative effect.

In allergic individuals outside the allergen season, most mast cells may reside well below the mucosal surface.²¹ The fate of tryptase released from the subepithelial cells, including its passage across membranes and cellular barriers, may be different in different airway conditions. In airways with extensive exudation of bulk plasma containing an abundance of binding and transport proteins, this process may dramatically affect the fate of subepithelial factors such as enzymes, mediators, and cytokines.²² For example, α_2 -macroglobulin is a multifactorial cytokine-binding protein.²³ We therefore suggest that in this study the reduced mucosal output of tryptase may be explained in part by the loratadine-induced inhibition of the plasma exudation response. (The lack of effect of loratadine on airway eosinophilia may support this interpretation; see below.) Indeed, a potential dependency on plasma exudation processes of factors found in airway lavage fluids may be worthy of general consideration in studies of inflammatory challenge and disease conditions.^{11, 22}

In confirmation of previous observations, loratadine significantly suppressed the present allergen challenge-induced nasal symptoms.⁴ The effect on nasal blockage was verified by peak expiratory flow rate measurements involving both the right and left nasal passages, although the allergen challenges were carried out in only the right nasal cavity. The results suggest that treatment with loratadine 20 mg orally once daily, in addition to its marked effect on sneezes and secretion, also reduces nasal blockage in acute allergic rhinitis. The oxymetazoline treatment carried out before the allergen challenges would have affected blockage scores and nasal peak expiratory flow rates equally in subjects receiving placebo and loratadine treatment.

The antihistamine cetirizine may reduce allergen-induced recruitment of eosinophils in human skin,²⁴ and a similar effect of cetirizine has also

been suggested to occur in the bronchial airways. Thus it has been reported that cetirizine treatment reduced the numbers of eosinophils in bronchoalveolar lavage fluid obtained during a late-phase response to allergen challenge.²⁵ In contrast, Klementsson et al.²⁶ demonstrated no such effect of cetirizine in allergen-challenged human nasal airways. This study, in which a nasal brush technique was used to obtain cell specimens, again demonstrated that allergen-induced nasal eosinophilia was unaffected by antihistamine (loratadine) treatment. Because mast cells may be involved in recruitment of eosinophils, the lack of effect of loratadine on eosinophil numbers in the samples obtained by the brush technique may argue against a general mast cell-stabilizing effect of this antihistamine drug.

In conclusion, this study demonstrates that loratadine inhibits the allergen challenge-induced mucosal output of α_2 -macroglobulin and tryptase, as well as the symptoms of allergic rhinitis. The data suggest that loratadine reduces the mediator-induced plasma exudation response of acute allergic airway inflammation. The effects of loratadine on the lavage fluid levels of α_2 -macroglobulin and tryptase may be due to antagonism of microvascular effects of histamine, or they may be due to both the antihistamine effects and a mast cell inhibitory action.

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