

The effect of terfenadine on unilateral nasal challenge with allergen

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To investigate the role of H_1 receptor-mediated effects in allergic rhinitis, we challenged 12 allergic volunteers with allergen 2 hours after administration of either placebo or 60 mg of terfenadine. Filter paper discs were used for the unilateral administration of allergen and the collection of nasal secretions. Secretion weights, levels of histamine in recovered nasal secretions, and nasal airway resistance (NAR) were measured for each nostril separately, and the number of sneezes was counted. After placebo treatment, allergen challenge led to significant increases in ipsilateral and contralateral secretion weights, ipsilateral histamine levels, ipsilateral NAR, and sneezing. Contralateral histamine levels were not elevated. H_1 antagonism with terfenadine markedly reduced the number of sneezes and partially decreased ipsilateral and contralateral secretion weights, without affecting the increase in NAR. Terfenadine premedication also lowered the amount of histamine in ipsilateral secretions after allergen challenge. Performing identical nasal challenges with a 10-fold lower dose of antigen produced similar results. Previous studies showed that terfenadine had no effect on methacholine provocation and completely abolished ipsilateral and contralateral secretion weights after histamine challenge. We conclude that sneezing after allergen challenge is caused almost exclusively by a reflex initiated through H_1 receptors and that H_1 antagonism has no influence on allergen-induced increases in NAR. Unilateral allergen challenge leads to bilateral increases in secretion weights, which are only partially inhibited by terfenadine, suggesting the involvement of mediators other than histamine in the nasosnasal reflex. As reported earlier, terfenadine also decreases allergen-induced histamine release after challenge with the highest dose of antigen. (J ALLERGY CLIN IMMUNOL 1994;93:594-605.)

Key words: Terfenadine, secretion weight, nasal airway resistance, histamine

H_1 receptor antagonists are the most frequently used drugs in the treatment of allergic rhinitis.¹ Newer members of this group, such as terfenadine, exert competitive H_1 antagonism without inducing anticholinergic side effects or crossing the blood-brain barrier.² Thus in addition to their clinical utility, they are useful probes for the investigation of the pathophysiologic events after allergen challenge. Furthermore, nonsedating an-

Abbreviations used

NAR: Nasal airway resistance
PNU: Protein nitrogen units

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tihistamines, including terfenadine, have properties, in addition to pure H_1 receptor antagonism, which may contribute to their efficacy.^{3, 4}

Evidence suggests that physiologic changes after nasal allergen challenge are partially mediated by neuronal reflexes. The prime example is sneezing, an event coordinating many parts of the respiratory system and resulting in an explosive exhalation. Another example is that unilateral nasal challenge with histamine, a mediator released after nasal antigen challenge, leads to the production of bilateral secretions. Nasal secretions originate mainly from the seromucous glands in the submucosa, from plasma via extravasation from submucosal vessels, and from water and electrolyte movement across the epithelium in response to osmotic and ionic gradients.⁵ Para-

sympatholytics partially inhibit histamine-induced ipsilateral secretions and almost completely inhibit contralateral secretions.^{6, 7} This suggests that ipsilateral secretions originate both from glands and plasma exudation, whereas contralateral secretions originate via a nasonasal reflex, the efferent limb of which is parasympathetically mediated.^{6, 7}

Nasal airway resistance (NAR), an objective measure of nasal congestion, is primarily determined by the tone of venous sinusoids in the submucosa. These specialized vessels are primarily under sympathetic control.⁸ An increase in adrenergic stimulation reduces NAR, as observed after the use of topical decongestants and exercise.⁹⁻¹¹ Moreover, NAR periodically fluctuates in both nostrils, whereas the total resistance remains constant. This nasal cycling is believed to be neuronally controlled by the central nervous system. Recent evidence suggests that neuropeptides, released during axon reflexes or sympathetic and parasympathetic nerve stimulation, may modulate the inflammatory response.¹² Therefore it seems that many aspects of nasal physiology are at least partially under neural control. However, the mechanisms by which allergen exposure influences the nervous system are poorly understood. Thus we investigated the effect of an H₁ receptor antagonist, terfenadine, on nasal reflexes after antigen challenge to distinguish H₁-mediated events from other contributing factors.

METHODS

Study design

A double-blind, placebo-controlled, randomized trial with terfenadine was performed to evaluate the effects of H₁ antagonism on allergen-induced changes in nasal physiology. Seven male and five female volunteers between 21 and 42 years of age participated in the first part of the study. Four male and four female volunteers between 21 and 42 years of age participated in the second part, in which a 10-fold lower concentration of antigen was used. All subjects were diagnosed as having seasonal allergic rhinitis by history and a positive intradermal skin test result to the appropriate allergen (10 protein nitrogen units [PNU]/ml or less). They had previously demonstrated a positive reaction to intranasal allergen challenge as defined by increases in symptoms, sneezing, and mediators in recovered nasal secretions. All subjects were free of symptoms at the time of the study and had not taken any medication except oral contraceptives within 4 weeks of the study. The study days were separated by at least 7 days. The trial was approved by the Institutional Review Board for Human Subjects Research of the Francis Scott Key Medical

Center, and each subject gave written informed consent before entering the study.

Disc method

The disc method was used for nasal allergen challenges and collection of nasal secretions. White filter paper discs (8 mm diameter, 1.2 mm thickness; punched out of Shandon filter cards, Shandon, Inc., Pittsburgh, Pa.) were used to administer the challenge solution to the middle portion of the anterior nasal septum, posterior to the mucocutaneous junction, and to collect nasal secretions from the same site and the corresponding area on the contralateral side by means of anterior rhinoscopy. Fifty microliters of allergen or diluent solution was pipetted onto a dry filter paper disc and applied to the nasal mucosa. Collection discs were placed into 1.5 ml microtubes (Sarstedt Inc., Newton, N.C.), and both were weighed before and after collection of secretions, allowing calculation of the weight of the absorbed secretions. Challenge discs remained in the nose for 1 minute; and collection discs for 30 seconds.⁶ Each weighed collection disc was eluted in 300 μ l of saline solution (0.9% sodium chloride [USP], Kendall McGaw Laboratories, Irvine, Calif.) for 24 hours at 4° C. The disc was then removed, and mediators in the eluate were measured.

Histamine measurement

Histamine was measured with a radioenzymatic assay sensitive to 250 pg/ml.¹³ The reliability and reproducibility of this method was demonstrated by the recovery of known volumes and concentrations of histamine from the discs (data not shown). The histamine values shown herein are total amounts of histamine recovered from each individual collection disc. These values were calculated by multiplying the measured concentration in the assay (in nanograms per milliliter) by the volume of the collected secretions plus the volume of the eluate (300 μ l). The recovery of histamine from a disc after addition of a histamine standard was not different in nasal secretions collected after placebo or terfenadine treatment.

Allergen solutions

Mixed grass (timothy, June, meadow fescue, and orchard grasses) or ragweed allergen extracts (Greer Laboratories, Lenoir, N.C.) at concentrations of 6667 PNU/ml and 667 PNU/ml were used. This equals 333 PNU and 33.3 PNU, or approximately 1.2 μ g and 0.12 μ g *Amb a* I for ragweed solutions, in 50 μ l used for challenge. To control for nonspecific irritation, challenges with the phenol-containing diluent (sterile phenol-buffered saline, Greer Laboratories) were performed before all allergen challenges.

Challenge procedure

Two hours before the allergen challenge, a single dose of 60 mg of terfenadine (Seldane) or placebo

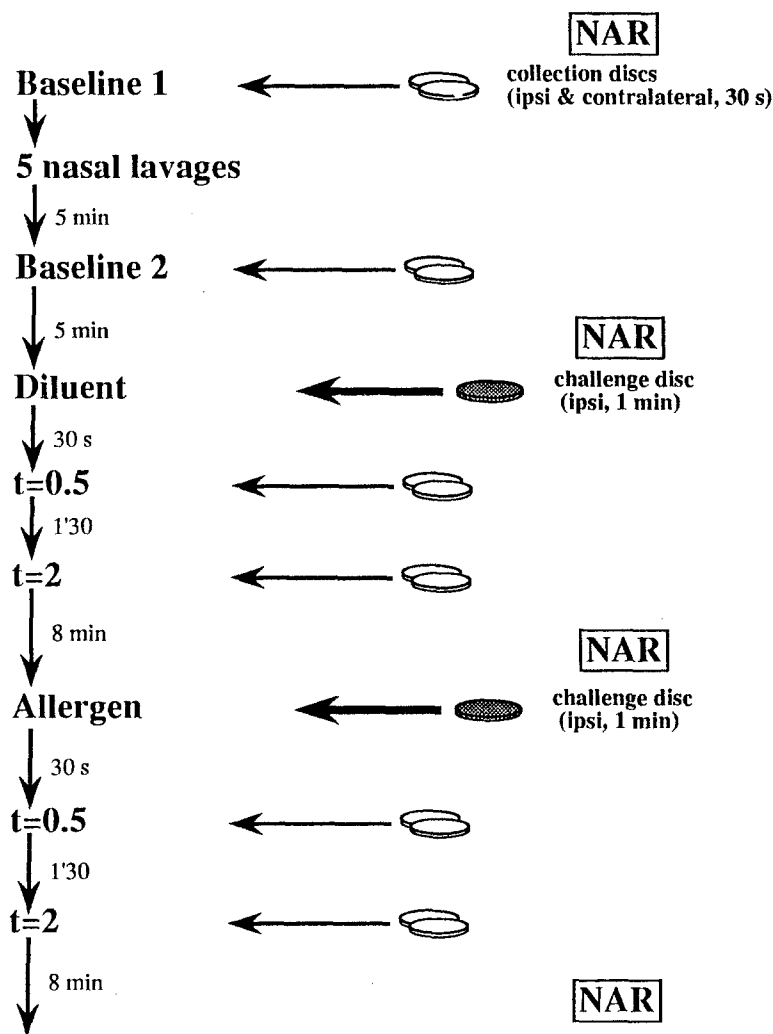


FIG. 1. Protocol of nasal allergen challenges with the disc method. Arrows indicate the time points of disc insertion in the nose. White pair of discs represent bilateral collection discs. Darker single discs represent unilateral challenge discs. The intervals between time points are shown to the right of the arrows.

(Lactose N.F., Amend Co., Irvington, N.J.) was orally administered to the volunteers in the form of blinded capsules.

The nasal cavities were inspected by means of anterior rhinoscopy to confirm the absence of nasal secretions before the challenge procedure. Then NAR was measured bilaterally with anterior rhinomanometry (Rhinomanometer A440 digital; Allergopharma Ganzler KG, Hamburg, Germany). Subsequently, the first collection discs were applied to measure baseline secretions and mediators (baseline 1). Five nasal lavages with 5 ml of physiologic saline solution at 37° C were performed to reduce levels of preexisting mediators to a stable baseline. Five minutes later, a second pair of collection discs was applied (baseline 2). NAR was measured at the end of the 5-minute period before the diluent challenge. Secretions were

collected 30 seconds and 2 minutes ($t = 0.5$; $t = 2$) after the removal of the diluent challenge disc with preweighed filter paper discs. At the end of the 8-minute period before allergen challenge, NAR was measured again. Allergen-induced nasal secretions were collected 30 seconds and 2 minutes after removal of the allergen challenge disc. Eight minutes later, NAR was measured (Fig. 1). The number of sneezes was counted during each interval.

Statistical methods

All data are presented as means $\pm$ SEM. For sneezing, secretion weights, and histamine values, the sums of the two time points after diluent and allergen challenges are shown, unless otherwise noted. Nonparametric statistics were used to compare placebo and drug

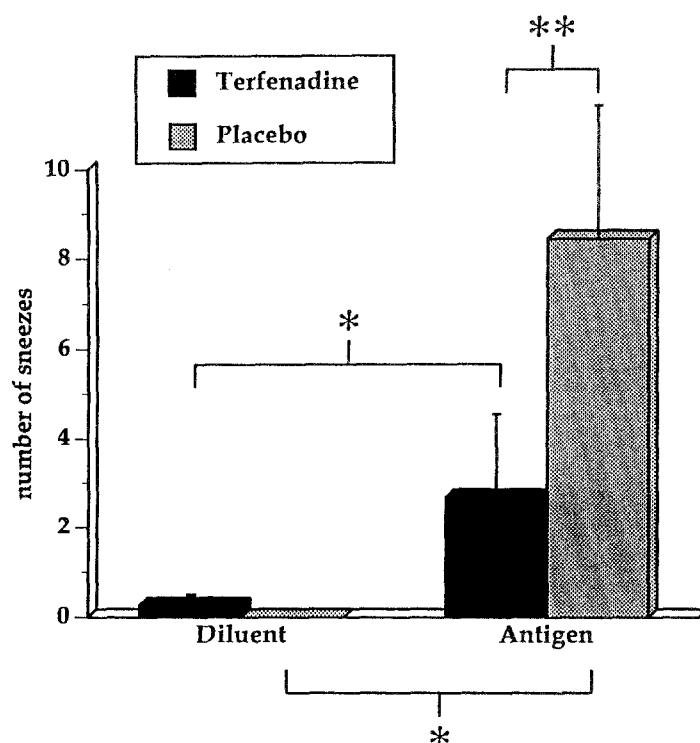


FIG. 2. Number of sneezes after intranasal unilateral challenge with 333 PNU of allergen. The number of sneezes significantly increased after allergen challenge compared with the number after diluent challenge after both placebo and terfenadine treatments. The number of sneezes was significantly reduced by terfenadine compared with placebo ($N = 12$). * $p < 0.05$ antigen versus diluent; ** $p < 0.05$ terfenadine versus placebo.

treatment and the responses to allergen challenge. Friedman analysis of variance and Wilcoxon matched pairs signed-rank tests were used. Two-tailed p values are reported. Unless otherwise noted, results from Wilcoxon tests are given. The statistical tests were performed on Macintosh computers (Apple Computers, Cupertino, Calif.) with Statview II software (Abacus Concepts, Berkeley, Calif.).

RESULTS

In placebo-treated volunteers, unilateral challenge with 333 PNU of allergen led to the typical changes in nasal physiology. The number of sneezes increased significantly compared with diluent (0 ± 0 vs 8.4 ± 3.0 , $p = 0.005$) (Fig. 2). NAR on the ipsilateral side increased from 0.7 ± 0.1 kPa/L/sec to 2.2 ± 0.9 kPa/L/sec ($p = 0.0044$) (Fig. 3, A). On the contralateral side, NAR remained unchanged compared with diluent (1.0 ± 0.3 kPa/L/sec to 1.1 ± 0.2 kPa/L/sec, $p = 0.41$) (Fig. 3, B). The weight of ipsilateral nasal secretions increased from 16.2 ± 3.0 mg after diluent challenge to 66.1 ± 6.0 mg after allergen challenge ($p = 0.0022$) (Fig. 4, A). Contralateral

secretion weights increased to 58.0 ± 5.7 mg from 15.4 ± 3.5 mg ($p \leq 0.05$), which was only slightly lower than ipsilateral secretion weights (Fig. 4, B). The amount of histamine in the ipsilaterally collected secretions increased from 2.76 ± 1.53 ng after diluent challenge to 9.55 ± 2.68 ng after allergen challenge ($p = 0.023$) (Fig. 5, A). Contralateral histamine values did not increase (2.78 ± 1.12 ng to 2.75 ± 0.54 ng, $p = 0.58$) (Fig. 5, B).

Terfenadine treatment decreased the number of sneezes after allergen challenge from 8.4 ± 3.0 to 2.7 ± 1.9 ($p = 0.0075$), but the number of sneezes still increased relative to the diluent challenge ($p = 0.027$) (Fig. 2).

The baseline and diluent values for ipsilateral NAR were not significantly different between terfenadine-treated and placebo-treated groups ($p > 0.16$). After allergen challenge with the subjects receiving terfenadine, ipsilateral NAR increased from 0.9 ± 0.3 kPa/L/sec to 2.4 ± 0.9 kPa/L/sec ($p = 0.0044$), which was not significantly different from placebo ($p = 0.67$) (Fig. 3, A). There was no significant difference between

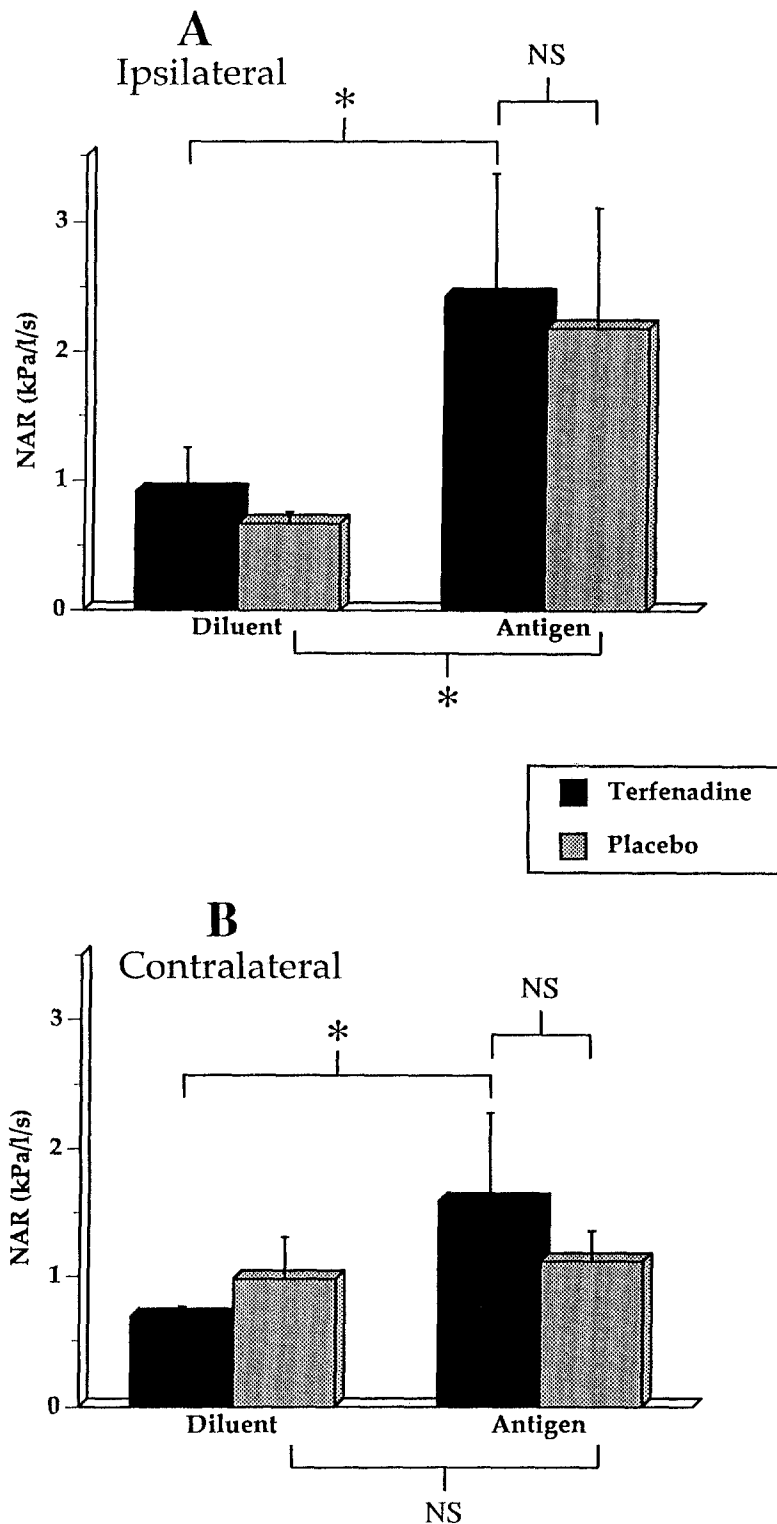


FIG. 3. NAR after intranasal unilateral challenge with 333 PNU of allergen. **A, Ipsilateral:** After both placebo and terfenadine treatment, NAR significantly increased after allergen challenge compared with that after diluent challenge. NAR after allergen challenge was not significantly different between terfenadine-treated and placebo-treated groups ($p = 0.67$). **B, Contralateral:** NAR significantly increased after allergen challenge compared with that after diluent challenge after terfenadine treatment but not in the placebo group. NAR after allergen challenge was not significantly different between terfenadine-treated and placebo-treated groups ($N = 12$). * $p < 0.05$ antigen versus diluent. NS, Not statistically significant.

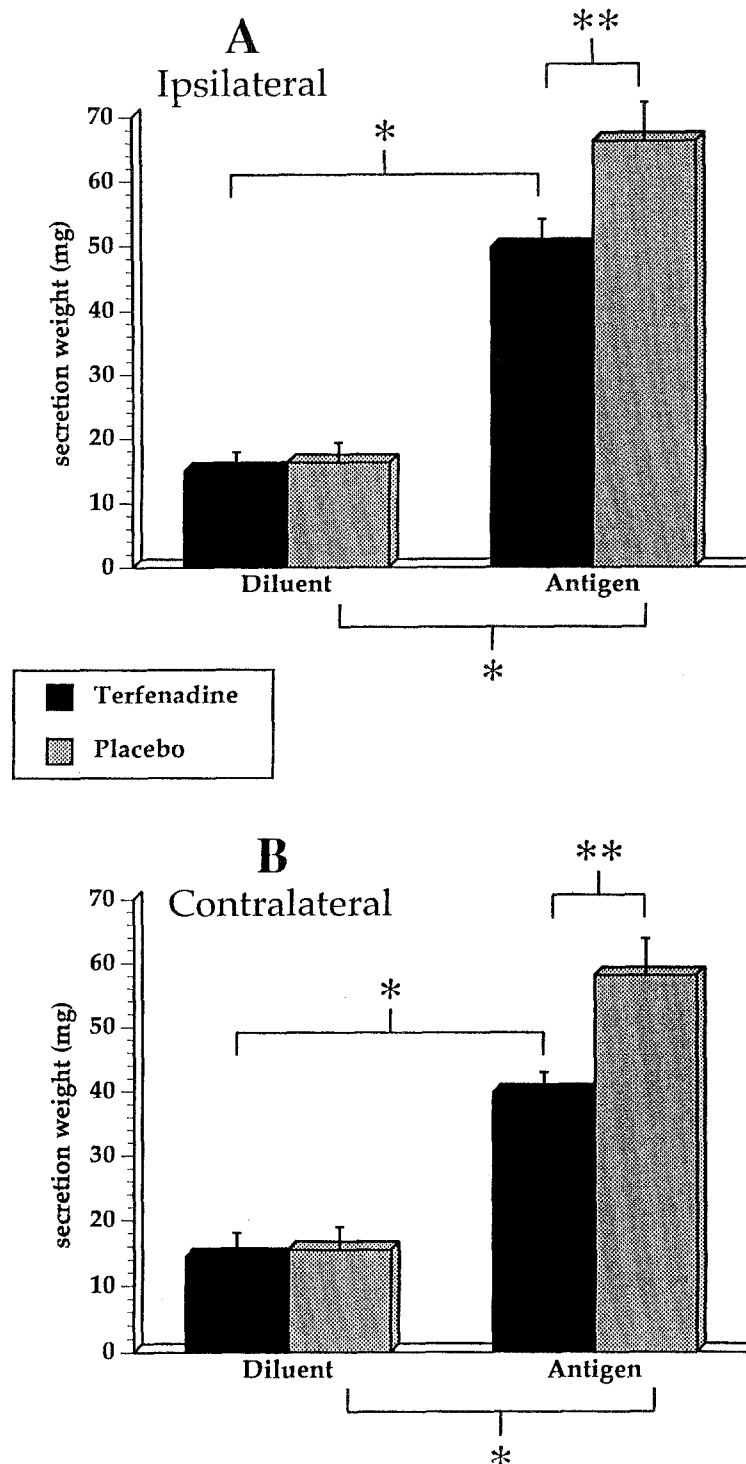


FIG. 4. Secretion weights after intranasal, unilateral challenge with 333 PNU of allergen. Sums of the two time points after diluent and allergen challenges are shown. **A, Ipsilateral:** Allergen challenge led to significant increases in secretion weights compared with diluent challenge both after placebo and terfenadine treatments. Terfenadine led to a significant reduction in allergen-induced secretion weights compared with placebo. Secretion weights after diluent challenge were not significantly different ($p = 0.66$). **B, Contralateral:** Allergen challenge led to significant increases in secretion weights compared with diluent challenge both after placebo and terfenadine treatments. Terfenadine led to a significant reduction in allergen-induced secretion weights compared with placebo. Secretion weights after diluent challenge were not significantly different ($p = 0.69$) ($N = 12$). * $p < 0.05$ antigen versus diluent; ** $p < 0.05$ terfenadine versus placebo.

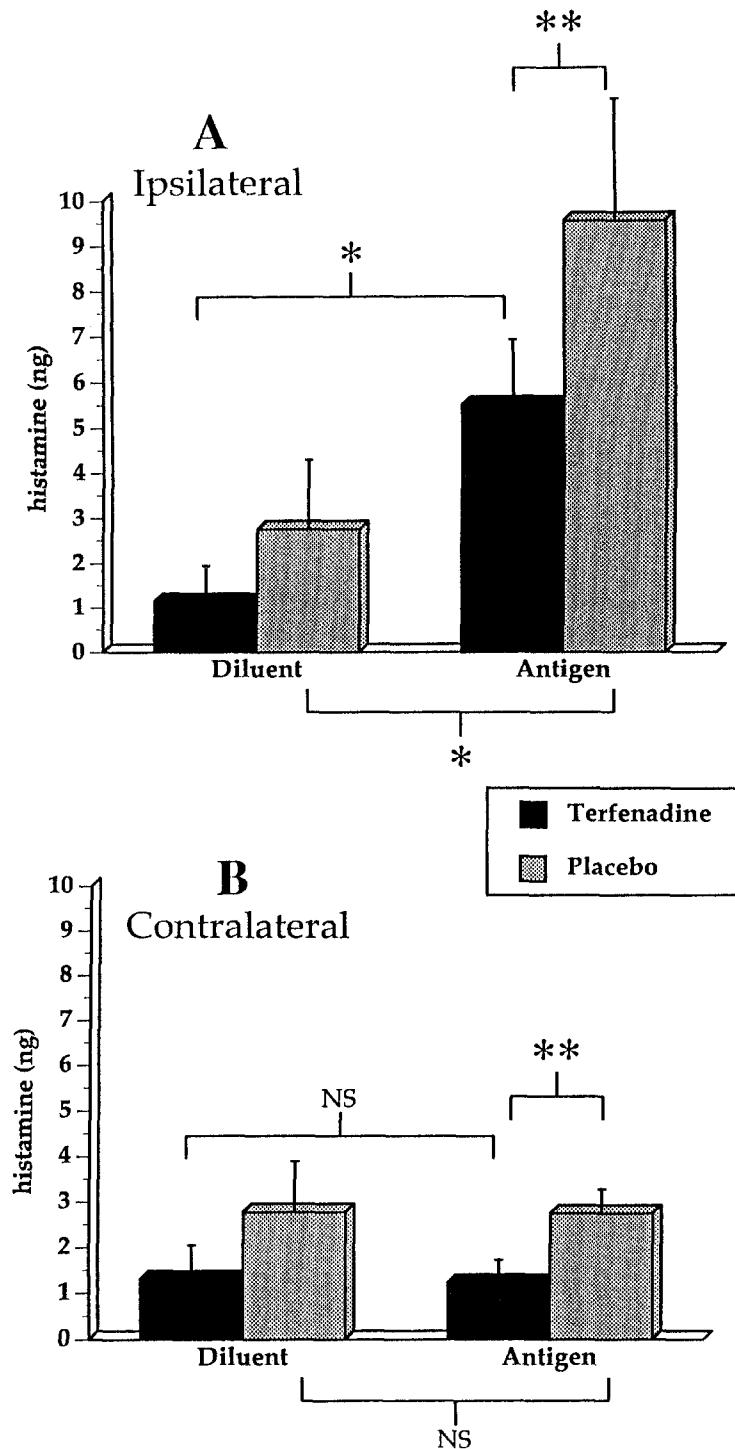


FIG. 5. Total amount of histamine in collected nasal secretions after intranasal, unilateral challenge with 333 PNU of allergen. Sums of the two time points after diluent and allergen challenges are shown. **A**, Ipsilateral: Histamine values were significantly increased compared with those after diluent challenge after both placebo and terfenadine treatments. Terfenadine caused a significant reduction in allergen-induced histamine release compared with placebo. Levels of histamine were not significantly different after diluent challenges ($p = 0.12$). **B**, Contralateral: Allergen challenge did not induce a significant increase in histamine after placebo or terfenadine treatments. The amount of histamine after diluent challenges was not significantly different between treatments ($p = 0.35$). After allergen challenge, histamine levels were significantly lower in the terfenadine-treated group ($N = 12$). * $p < 0.05$ antigen versus diluent; ** $p < 0.05$ terfenadine versus placebo. NS, Not statistically significant.

the contralateral NAR of the placebo-treated and terfenadine-treated groups at any of the measured time points ($p > 0.78$). In contrast to placebo, allergen caused a significant increase in contralateral NAR over diluent (1.6 ± 0.7 kPa/L/sec vs 0.7 ± 0.1 kPa/L/sec, $p = 0.026$) when terfenadine was given (Fig. 3, B).

Nasal secretion weights after diluent challenge were similar between the treatments ($p > 0.66$). Ipsilateral nasal secretion weights after allergen challenge were significantly reduced by terfenadine (66.1 ± 6.0 mg to 49.5 ± 4.5 mg, $p = 0.041$) (Fig. 4, A). Allergen-induced ipsilateral secretion weights, however, were significantly higher than the diluent values (49.5 ± 4.5 mg vs 14.9 ± 3.0 mg, $p = 0.0029$) in subjects treated with terfenadine. Contralateral secretion weights after allergen challenge in patients receiving terfenadine were also significantly increased over those after diluent challenge (39.7 ± 3.3 mg vs 14.4 ± 3.6 mg, $p = 0.0029$). Terfenadine caused a significant reduction in allergen-induced contralateral secretion weights ($p = 0.0096$) (Fig. 4, B).

Although the increase over values after diluent challenge was still significant ($p = 0.0022$), terfenadine reduced the amount of histamine in ipsilaterally collected secretions after allergen challenge from 9.55 ± 2.68 ng to 5.50 ± 1.42 ng ($p = 0.0019$) (Fig. 5, A). In both groups contralateral histamine values did not increase after allergen challenge ($p = 0.66$, compared with diluent) (Fig. 5, B). The contralateral histamine values after allergen challenge, although not significantly elevated over those after diluent challenge ($p > 0.66$), were reduced by administration of terfenadine ($p = 0.041$).

After completing these challenges, we were surprised by the relatively small degree of reduction that terfenadine caused in allergen-induced secretion weights. Therefore we decided to repeat that study with a 10-fold lower dose of antigen (33.3 PNU). Eight volunteers participated in the study in which the same protocol as described above was used.

The results were very similar: terfenadine caused a marked reduction in the number of sneezes after allergen challenge from 5.0 ± 1.6 after placebo administration to 0.6 ± 0.3 ($p = 0.012$). The terfenadine-treated group did not show a significant increase in the number of sneezes after allergen challenge ($p = 0.10$), whereas the placebo group did ($p = 0.012$) (Fig. 6). Ipsilateral NAR increased significantly after allergen challenge only in the terfenadine-treated group ($p = 0.036$), not in the placebo group

($p = 0.29$), and it was significantly higher in volunteers treated with terfenadine ($p = 0.046$). The contralateral NAR did not show significant changes in either group (placebo: $p > 0.09$; terfenadine: $p = 0.34$) and did not differ between the two groups ($p > 0.069$).

The lower dose of antigen caused significant increases in ipsilateral secretion weights compared with diluent challenge after both placebo and terfenadine administration ($p = 0.012$, $p = 0.012$). Terfenadine significantly reduced the allergen-induced ipsilateral secretion weights from 47.1 ± 5.0 mg to 30.7 ± 6.4 mg ($p = 0.049$) (Fig. 7, A). Contralateral secretion weights also significantly increased after allergen challenge in both groups ($p = 0.017$ for placebo, $p = 0.049$ for terfenadine), but terfenadine did not cause a significant reduction ($p = 0.33$) (Fig. 7, B).

The amount of histamine in the ipsilateral nasal secretions increased from 1.6 ± 0.8 ng after diluent challenge to 5.2 ± 2.2 ng after allergen challenge in the placebo-treated group. These changes nearly reached statistical significance ($p = 0.063$). Ipsilateral histamine levels also increased after allergen challenge in the terfenadine-treated group (1.4 ± 0.8 ng vs 4.2 ± 1.2 ng, $p = 0.043$, compared with diluent). Terfenadine did not significantly reduce ipsilateral histamine values after allergen challenge ($p = 0.40$). On the contralateral side, histamine values did not increase significantly in either group after allergen challenge ($p > 0.31$), and there was no significant difference between the two treatments ($p > 0.24$).

DISCUSSION

We performed nasal allergen challenges with filter paper discs. The localized, unilateral allergen challenges produced strong reactions in the volunteers, as demonstrated by the number of sneezes, the large amount of secretions, and the increases in NAR. The disc method allowed us to collect nasal secretions independently in both nostrils without interfering with the nasal physiology, as experienced in other collection methods. The nasal lavage technique, for example, invalidates the measurement of NAR because of the application of decongestants. Furthermore, secretions can be collected only bilaterally, and it is not possible to quantify amounts. The technique used in this study bypasses these disadvantages. Although only relatively small volumes of nasal secretions are collected, histamine and other mediators can be measured in sensitive assays. The disc method has some disadvantages. The small

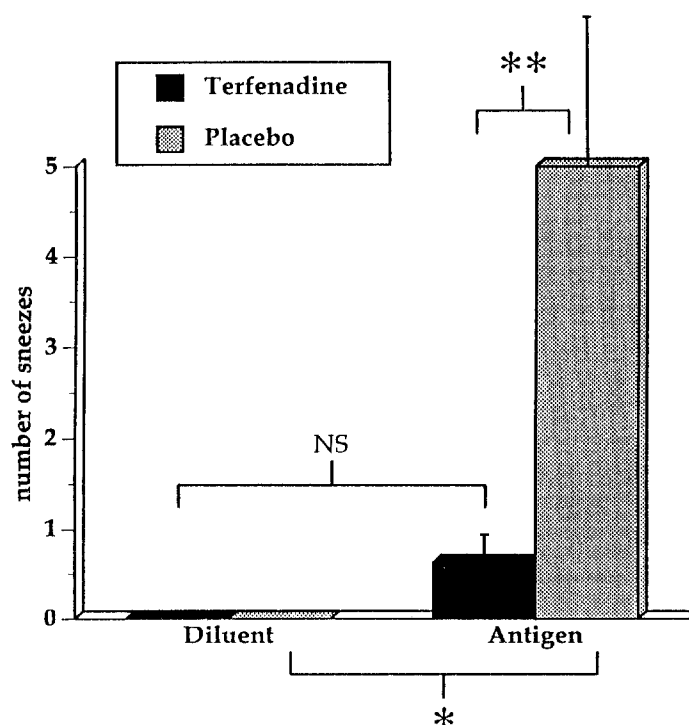


FIG. 6. Number of sneezes after intranasal unilateral challenge with 33.3 PNU of allergen. Allergen challenge led to a significant increase in the number of sneezes in volunteers treated with placebo. After terfenadine premedication, there was no significant increase in the number of sneezes after antigen challenge compared with the number after diluent challenge. Terfenadine significantly reduced the number of sneezes after allergen challenge compared with placebo ($N = 8$). * $p < 0.05$ antigen versus diluent; ** $p < 0.05$ terfenadine versus placebo. NS, Not statistically significant.

volume of secretions collected limits the number of biologic markers that can be measured simultaneously. The potential effect of mechanical stimulation must be controlled, and the limited area challenged may overemphasize reflex activity. As with all models, the data must be interpreted with an understanding of the techniques used.

After allergen challenge, all allergic volunteers sneezed when they were premedicated with placebo. Most of them did not sneeze at all after terfenadine treatment. This highly significant and almost complete inhibition was even more pronounced when the dose of antigen was reduced. Apart from histamine, serotonin is the only other inflammatory mediator known to induce sneezing after intranasal application.¹⁴ Although histamine and serotonin show some cross-reactivity at the level of their receptors,¹⁵ terfenadine has no antiserotonergic activity.¹⁶ A major role for serotonin in the sneezing response therefore seems unlikely. We conclude that the sneezing reflex in the allergic reaction is almost exclusively initiated by the action of histamine via H_1 receptors.

Terfenadine significantly reduced nasal secretion weights after allergen challenge. This is not caused by possible anticholinergic properties of this antihistamine, because previous experiments demonstrated that premedication with terfenadine did not inhibit secretions generated by methacholine challenge.⁶ Although the reduction of ipsilateral and contralateral secretion weights after allergen challenge by terfenadine was significant, its effect was relatively small compared with abolishing the increase in secretion weights after unilateral intranasal histamine challenge.⁶ Therefore the involvement of H_2 or H_3 receptors in the modulation of histamine-evoked nasal secretions is unlikely. In a model of histamine-induced nasal secretions in guinea pigs, H_1 blockade caused very similar results, whereas H_2 blockade had no effect.¹⁷ Other inflammatory mediators released after allergen challenge probably account for the nasal secretions that were not inhibited by terfenadine premedication. These mediators are also capable of inducing a naso-nasal reflex, because significantly increased secretion weights on the contralateral side still oc-

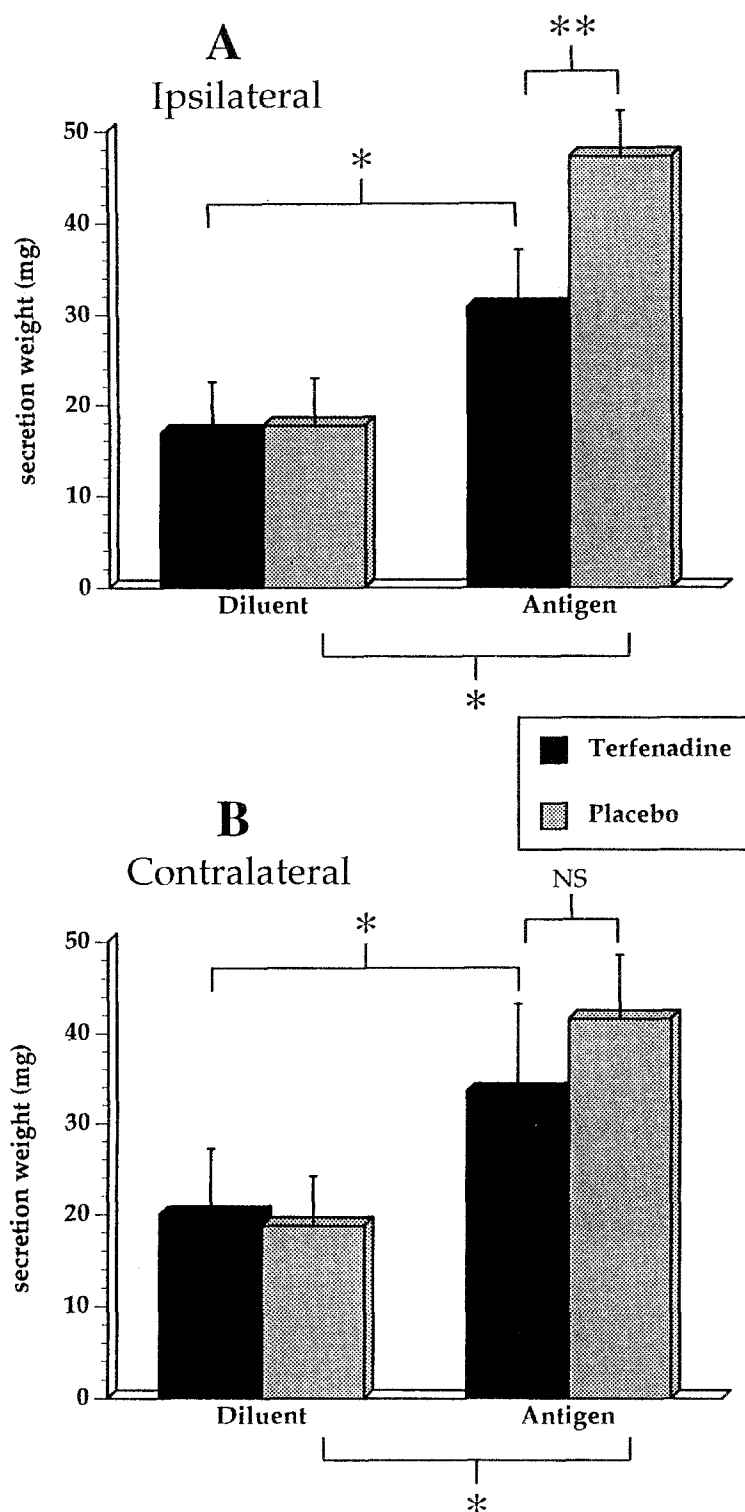


FIG. 7. Secretion weights after intranasal, unilateral challenge with 33.3 PNU allergen. Sums of the two time points after diluent and allergen challenges are shown. **A**, Ipsilateral secretion weights increased significantly after allergen challenge in both groups. Terfenadine caused a significant reduction in allergen-induced secretion weights. **B**, Contralateral secretion weights were significantly higher after allergen challenge than after diluent challenge in both groups. Terfenadine did not significantly reduce allergen-induced secretion weights ($p = 0.33$) ($N = 8$). * $p < 0.05$ terfenadine versus placebo. NS, Not statistically significant. ** $p < 0.05$ terfenadine versus placebo.

curred after H_1 antagonism in our study. The efferent limb of the reflex is parasympathetically mediated because contralaterally applied atropine completely inhibits increases in contralateral secretion weights after allergen challenge (data not shown). It is unlikely that histamine released after allergen challenge causes nasal secretions by direct action on nasal glands because radiographic studies did not detect H_1 receptors on them¹⁸ and histamine does not stimulate nasal glandular tissue *ex vivo*.¹⁹ However, not all results of clinical studies are consistent with these findings.

Measurement of glandular and vascular markers in allergen-induced nasal secretions showed that they also originate from vascular leakage.^{3, 20} The vessels in the submucosa bear H_1 receptors,¹⁸ and nasal histamine challenge leads to increased albumin levels in the secretions.^{3, 17} The allergen-induced albumin increase can be reduced by terfenadine,³ suggesting that histamine increases vascular permeability by direct action on H_1 receptors on nasal vessels. Nasonasal reflexes do not seem to be involved in this event, because the contralateral secretions after allergen (and histamine) challenge are mainly of glandular origin and are not associated with increases in albumin.⁷ The possibility of axon reflexes altering the vascular reactions after allergen challenge should not be excluded,²¹ but recent studies suggest that capsaicin does not increase vascular leakage in human beings,^{22, 23} although direct challenge with substance P causes an increase in albumin leakage.²⁴

Unilateral nasal allergen challenge led to ipsilateral increases in NAR that were not influenced by terfenadine, suggesting that these changes are not uniquely mediated through H_1 receptors. Studies on the increase of NAR after histamine challenge demonstrated reductions only with combined H_1 and H_2 antagonism, whereas the antagonists were ineffective when used individually.^{25, 26} Other mediators may be more important in the induction of NAR increases in the allergic reaction. Leukotrienes, prostaglandins, and kinins have all been demonstrated to increase NAR after intranasal application.²⁷⁻²⁹ The role of reflexes in these changes remains undetermined, but it is clear that the venous sinusoids, which are the main determinant of NAR, are controlled by sympathetic nerves.⁸ In this study we found inconsistent increases in NAR on the contralateral side that reached significance only with the higher dose of allergen and after terfenadine premedication, but

it is possible that we did not obtain measurements long enough after challenge to detect these changes. The reason for this increase in NAR on the contralateral side after terfenadine premedication is not apparent.

Unilateral nasal allergen led to histamine release on the ipsilateral side only. Thus mast cells are directly degranulated only at the site of challenge, and the increase in recovered histamine is not a reflection of increased secretions, the latter being supported by the contralateral increase in secretions without an increase in recovered histamine. The amount of ipsilaterally secreted histamine was significantly reduced by a single dose of terfenadine. Prior studies showed that continuous dosage of the same drug decreases allergen-induced histamine levels^{3, 30} in recovered nasal lavages. The mechanism through which this effect occurs remains unclear, although it has been shown that some antihistamines, mainly of the tricyclic class, decrease histamine release from basophils and mast cells *in vitro*.³¹ One may also hypothesize that the possible activation of mast cells by axon reflexes on the ipsilateral side may be reduced by antagonizing H_1 receptors on sensory nerves. We do not suspect that neuronal mechanisms play a role because of the contralateral findings and because other *in vivo* investigations with the H_1 antagonists cetirizine,³² azelastine,³³ ketotifen,³⁴ and diphenhydramine³⁵ did not demonstrate reduced allergen-induced histamine release.

The effects of terfenadine observed in this study correlate closely with the results of several clinical trials: terfenadine markedly reduced sneezing and decreased rhinorrhea, whereas symptoms of nasal stuffiness did not decrease.^{36, 37} This allergen challenge model involving the local application of small paper discs appears to provide reliable information on the simultaneous effects of pharmacologic modulation on nasal physiology and mediator release.

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