Antiallergic properties of the second-generation H_1 antihistamines during the early and late reactions to antigen

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Some of the second-generation H_1 antihistamines reduce the bronchoconstrictor response after exercise and antigen challenge. For example, terfenadine causes a slight but significant increase in forced expiratory volume after 1 second. At doses of 120 and 240 mg, terfenadine has a protective effect against asthma induced by ultrasonic nebulized distilled water and cold air hyperventilation challenge. Certain other newer antihistamines, such as ketotifen, azelastine, and cetirizine, have additional antiallergy properties. These effects include inhibition of eosinophil, basophil, and neutrophil migration and platelet-activating factor–induced eosinophil accumulation in skin. The ability of cetirizine (and perhaps other antihistamines) to inhibit these responses at usual therapeutic doses may be useful in investigating the late allergic reaction. (J ALLERGY CLIN IMMUNOL 1992;90:720-5.)

Key words: *Antigen challenge, antihistamines, platelet-activating factor, asthma, bronchoconstriction, azelastine, cetirizine, ketotifen, terfenadine*

This article reviews some of the non-H_1 effects of second-generation antihistamines and examines some of the mechanisms of these effects on the late allergic reaction. These medications have a mild beneficial effect in patients with asthma. The first-generation antihistamines had relatively weak antihistaminic effects and had significant anticholinergic and sedative side effects.

Although the approved product labeling states that antihistamines are contraindicated or to be used with caution in patients with asthma because of an alleged drying effect on secretions, nearly all physicians recognize that the chances of exacerbating asthma with antihistamines are practically nil.

EXERCISE-INDUCED ASTHMA

One of the apparent non-H_1 effects of antihistamines was first described in patients with asthma by Patel in 1984[1] when he showed that terfenadine significantly inhibits EIA. Given at a dosage of 60 mg, terfenadine resulted in a 17% inhibition of EIA. Higher doses of 120 or 180 mg inhibited EIA by 30% and 32% respectively. Several agents in addition to antihistamines, including calcium channel blockers and α-adrenergic blockers, inhibit EIA but do not seem to be particularly effective in controlling asthma not induced by exercise.

Abbreviations used

EIA:	Exercise-induced asthma
FEV_1:	Forced expiratory volume in 1 second
LTC_4:	Leukotriene C_4
EPO:	Eosinophil peroxidase
PAF:	Platelet-activating factor
FMLP:	Formyl-methionyl-leucyl-phenylalanine

IMPROVED FEV_1

An interesting observation first reported by Rafferty and Holgate[2] was that terfenadine improves resting FEV_1 values in patients with allergic asthma (Table I). In this 1987 study involving 19 such patients, they reported statistically significant improvements in FEV_1 of 9.0%, 9.5%, and 10.2% 2 hours after doses of 60, 120, and 180 mg of terfenadine, respectively. Even 60 mg of terfenadine significantly improved FEV_1 ($p < 0.05$). In another study Patel and Ghosh[3] reported that 120 or 180 mg of terfenadine resulted in a 10% to 12% improvement in FEV_1.

The effect of an antihistamine on FEV_1 depends on the population that one is studying, the degree of potential reversibility, and the amount of histamine that may be in the lower airways of these patients. For example, in one study we observed a 5% improvement in FEV_1 3 hours after 120 mg of terfenadine in one group of subjects with asthma,[4] whereas in another group of nine male patients with asthma, a 17% improvement occurred 3 hours after the same dose of terfenadine.[5] If terfenadine is added to a muscle bath, it does not relax human airway smooth muscle, and thus is not a direct bronchodilator. I conceive

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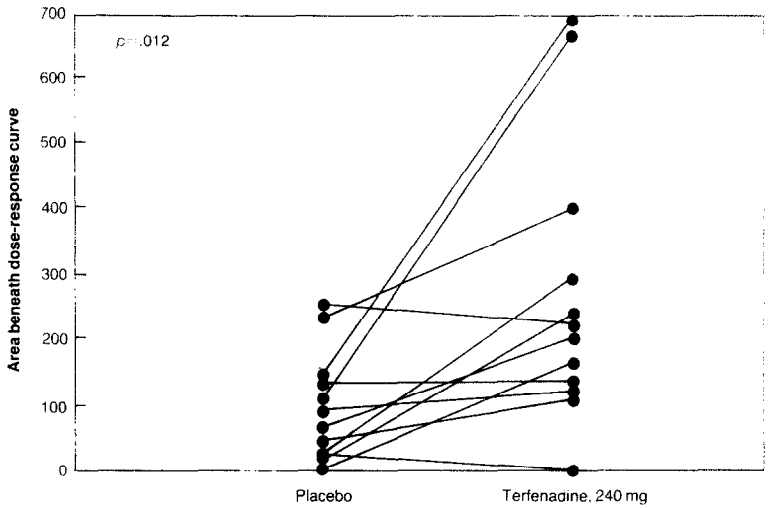

FIG. 1. In 12 patients with asthma, a 240 mg dose of terfenadine offered significant ($p = 0.012$) protection against challenge with ultrasonic nebulized distilled water. (From Hopp RJ, Bewtra AK, Nair NM. Effect of terfenadine on the bronchoconstriction induced by ultrasonically nebulized distilled water. Ann Allergy 1988;61:13-6.)

TABLE I. Effect of terfenadine on resting FEV_1

	Pretreatment	2 hr Posttreatment	Change (%)	*p*
Placebo	2.93 ± 0.36	2.82 ± 0.35	−3.8	NS
Terfenadine, 60 mg	2.99 ± 0.42	3.26 ± 0.41	+9.0	<0.05
Terfenadine, 120 mg	2.95 ± 0.35	3.23 ± 0.33	+9.5	<0.01
Terfenadine, 180 mg	2.94 ± 0.35	3.24 ± 0.34	+10.2	<0.01

From Rafferty P, Holgate ST. Am Rev Respir Dis 1987;135:181-90.
NS, not significant.

of it more as an "antibronchoconstrictor." This effect results from inhibiting endogenous histamine and thus inhibiting the tone in asthmatic airways that is partially attributable to histamine.

I believe that "antibronchoconstrictor" effect is being confirmed by the current use of leukotriene antagonists. The LTD_4 receptor antagonists also improve pulmonary function by a comparable degree, as much as 20%, even though they are not bronchodilators in the classic sense in vitro.[6] This finding suggests that histamine as well as leukotrienes provide airway tone in patients with asthma and that use of specific receptor antagonists for these mediators improves pulmonary function.

COLD AIR HYPERVENTILATION AND NEBULIZED DISTILLED WATER

We studied the effect of terfenadine on cold air hyperventilation challenge, which is a model similar to EIA, except that subjects do not have to exercise.[7] There was a modest but significant 5% improvement in FEV_1 with 120 and 240 mg of terfenadine between the second and fourth hour, which was the duration of the study.

In these same 12 patients with asthma, we did another challenge with the use of ultrasonic nebulized distilled water, also called fog challenge.[4] In this study subjects who received the 240 mg dose of terfenadine experienced a significant protection against the nebulized water challenge ($p < 0.012$) (Fig. 1). The area beneath the dose-response curve was significantly increased after the administration of 240 mg of terfenadine. The response after 180 mg of terfenadine approached significance ($p < 0.06$).

With exercise-, fog-, or cold air–induced asthma or with hypertonic saline solution challenges, a change occurs in the osmolarity and the ion composition of the airway periciliary fluid. Bronchial mast cells may degranulate in response to these changes in osmolarity or ion composition. EIA, cold air hyperventilation, or fog challenges are partially attenuated by terfenadine.

However, some difference exists between exercise and cold air in that exercise results in an elevated

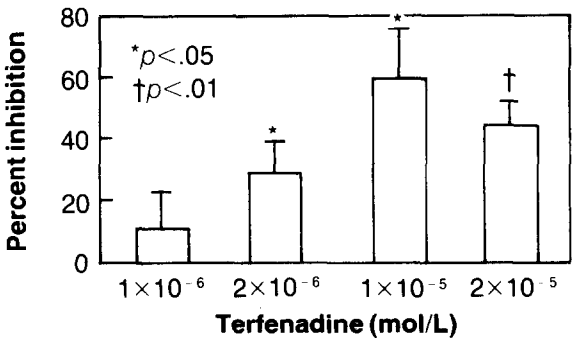

FIG. 2. At concentrations of 2×10^{-6} mol/L ($p < 0.05$) and 1×10^{-5} mol/L ($p < 0.01$), terfenadine significantly inhibited histamine release induced by anti-IgE. (From Nabe M, et al. Effect of terfenadine on mediator release from human blood basophils and eosinophils. Clin Exp Allergy 1989;19:515-20, by permission of Blackwell Scientific Publications.)

serum neutrophil chemotactic factor. To the best of my knowledge, this elevation has not been reported with cold air hyperventilation challenges. This difference suggests that they are not equivalent challenges in that regard. Whether histamine is released in exercise-induced asthma is controversial.

RELEASE OF HISTAMINE AND LTC_4

In another group of 10 patients with asthma, we evaluated mediator release from blood basophils with the use of anti-IgE as the stimulus of histamine release.[8] In this study we evaluated terfenadine over a concentration range to measure the percent inhibition of histamine release. At a concentration of 2×10^{-6} mol/L, terfenadine significantly inhibited histamine release, and at a higher concentration there was even greater inhibition (Fig. 2). The concentration of 2×10^{-6} mol/L approximates the blood levels of terfenadine and the first metabolite of terfenadine after doses of 180 or 240 mg.

Rafferty et al.[9] studied bronchoconstriction induced by various modalities. They observed that 180 mg of terfenadine resulted in 100% inhibition of histamine-induced bronchoconstriction. Compared with the placebo control, histamine caused a 30% decrease in FEV_1 (Fig. 3). After allergen challenge, there was approximately a 35% decrease in FEV_1 in subjects who received placebo. In those patients who received 180 mg of terfenadine, there was significant (50%) protection against an immediate allergen challenge during the 40 minutes in which they were observed.

With adenosine monophosphate challenge, there was approximately an 86% protection with terfenadine. Adenosine represents an indirect bronchial challenge, perhaps in the same category as exercise, cold air, and fog challenge. In contrast with histamine, adenosine is not a direct bronchoconstrictor but works through an indirect mechanism.

Nabe et al.[8] also looked at LTC_4 production from human eosinophils. The calcium ionophore A23187 was used to stimulate LTC_4 production. In these studies a 2×10^{-5} mol/L concentration of terfenadine caused inhibition of LTC_4 synthesis (Fig. 4). I hasten to add that the calcium ionophore A23187 is a nonphysiologic, powerful agent to stimulate LTC_4. We have studies now in progress to evaluate more physiologic stimuli of leukotriene synthesis.

In summary, the antihistamines evaluated in these studies reduce the bronchoconstrictor response after exercise and antigen challenge and in some clinical studies they show varying degrees of long-term efficacy in patients with asthma. Thus they may be useful additions to standard asthma therapy.

OTHER ANTIALLERGIC EFFECTS OF ANTIHISTAMINES

The antihistamines ketotifen, azalastine, and cetirizine have some additional antiallergic properties. Togias et al.[10] studied nasal allergen challenge and measured mediators in the nasal lavage fluid of patients with allergic rhinitis. The histamine released in the nasal secretion was inhibited by terfenadine but not by cetirizine (Table II). In contrast, cetirizine did inhibit the release of LTC_4 in the nasal secretions. Terfenadine has not been studied in this regard.

Charlesworth et al.[11] also evaluated the effect of cetirizine on the allergen-induced dermal response by using skin chambers. They examined the number of eosinophils and other leukocytes in vivo over time in this skin blister model. After the administration of placebo, there was a progressive increase in the number of eosinophils that migrated into the skin chamber. This influx was significantly inhibited by 20 mg of cetirizine per day for 2 days, particularly at 8 hours. Charlesworth et al. have now followed these subjects up to 12 hours and found that cetirizine also significantly inhibits the influx of basophils and neutrophils.

EOSINOPHIL CHEMOTAXIS

In pursuing studies of the effect of cetirizine, we looked at the effect of cetirizine on EPO release from eosinophils stimulated either with PAF or FMLP.[12] PAF and FMLP produced a modest but significant increase in EPO. We could not see any inhibition of EPO release with cetirizine. However, when we studied the effect of cetirizine on PAF-induced eosinophil chemotaxis in 13 subjects, beginning at a concentration of 10 nmol/L, cetirizine significantly inhibited PAF-induced eosinophil chemotaxis, apparently in a dose-related manner.

When we used FMLP to induce eosinophil chemotaxis, the cetirizine effect did not appear to be dose

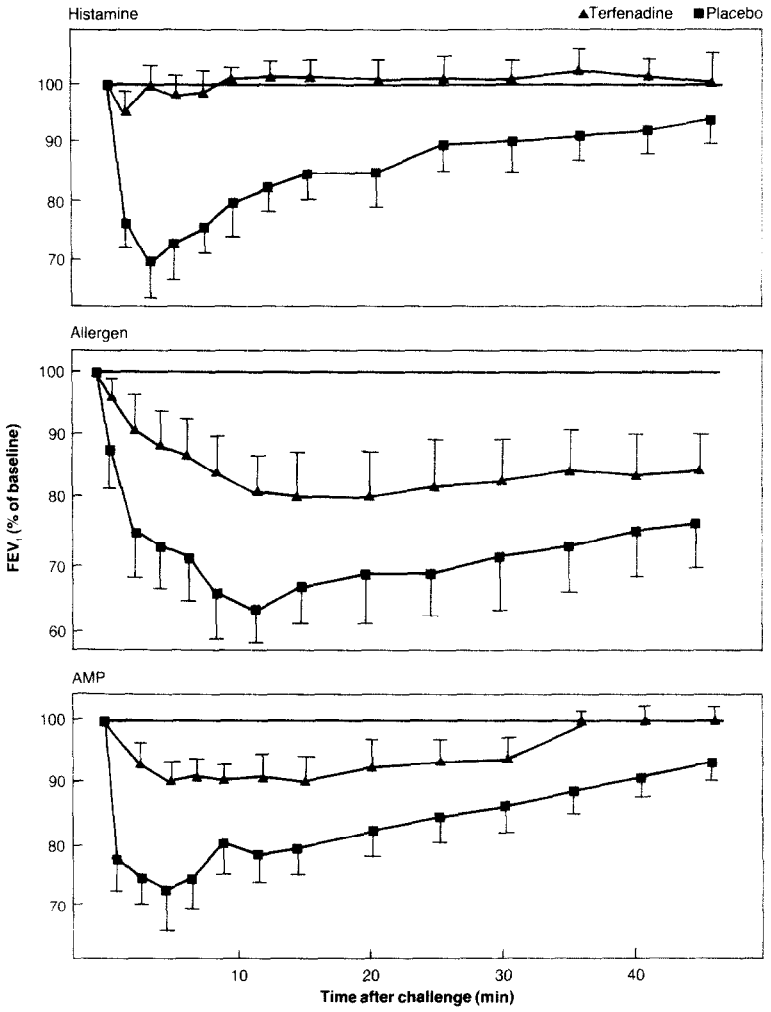

FIG. 3. Terfenadine at a dose of 180 mg produced 100% inhibition of histamine-induced bronchoconstriction and significant protection against allergen-induced bronchoconstriction. (From Rafferty P, et al. The contribution of histamine to immediate bronchoconstriction proved by inhaled allergen and adenosine 5′ monophosphate in asthma. Am Rev Respir Dis 1987;136:369-73.)

related. It achieved statistical significance in inhibiting eosinophil chemotaxis only at the 0.1 μmol/L concentration of cetirizine. As a control, we looked at the effect of a specific PAF antagonist, WEB-2086, which demonstrated a dose-related inhibition of eosinophil chemotaxis in both normal subjects and in patients with asthma.

WHEAL FORMATION AND ERYTHEMA

The effect of cetirizine on PAF or allergen in the skin was reported by Fadel et al.[13] They observed a significant inhibition of wheal formation with cetirizine, whether it was induced by pollen or by PAF. They used serum albumin as a control.

Cetirizine also significantly inhibited erythema induced in the skin by pollen or PAF in this model system. They also assessed the number of eosinophils accumulating in the skin window at 24 hours. Cetirizine significantly inhibited the percentage of eosin-

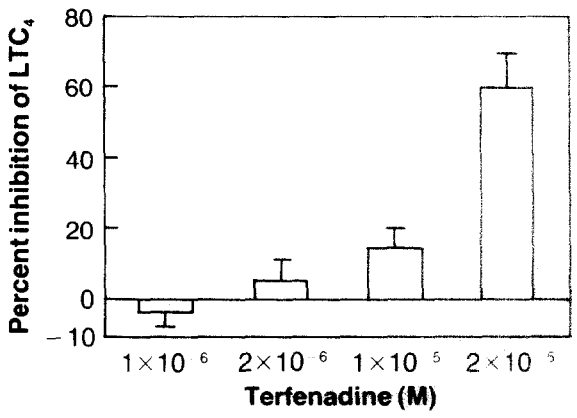

FIG. 4. At a concentration of 2×10^{-5} mol/L, terfenadine significantly inhibited synthesis of LTC_4 in human eosinophils. (From Nabe M, et al. Effect of terfenadine on mediator release from human blood basophils and eosinophils. Clin Exp Allergy 1989;19:515-20, by permission of Blackwell Scientific Publications.)

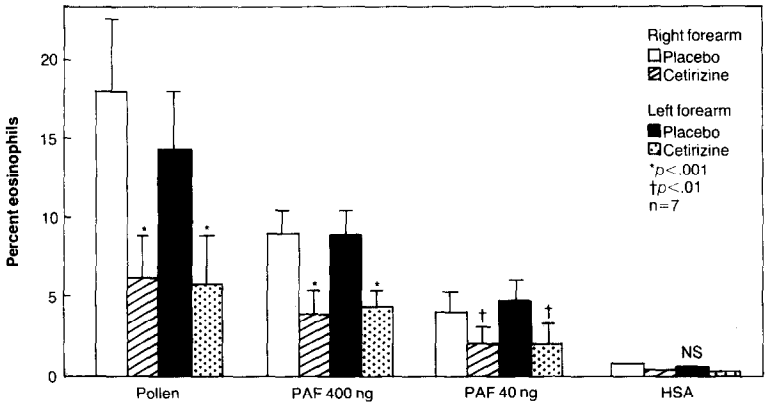

FIG. 5. Twenty-four hours after intradermal challenge with pollen and PAF, cetirizine significantly inhibited accumulation of eosinophils in a skin chamber model. *HSA,* Human serum albumin; *NS,* not significant. (From Fadel R, et al. In vivo effects of cetirizine on cutaneous reactivity and eosinophil migration induced by platelet activating factor [PAF-acether] in man. J ALLERGY CLIN IMMUNOL 1990;86:314-20.)

TABLE II. Effect of systemically administered antihistamines on nasal antigen challenge of allergic individuals

	Terfenadine	Cetirizine
Overall symptoms	↓	↓
Sneezing	↓	↓
Histamine in nasal secretions	↓	↔
TAME esterase(s) in nasal secretions	↓	↓
LTC_4 in nasal secretions	ND	↓

From Togias AG, Proud D, Kagey-Sobotka A, Freidhoff L. The in vivo and in vitro effect of antihistamines on mast cell mediator release: a potentially important property in the treatment of allergic disease. Ann Allergy 1989;63:467-9.

ophils elicited by pollen challenge or by PAF challenge (Fig. 5).

Hennocq and Vargaftig[14] observed that injection of PAF into the skin elicits eosinophils and a late reaction in atopic subjects but not in nonatopic subjects. In the study reported by Fadel et al.,[13] all subjects were atopic.

I am not aware of any studies in humans in which PAF has elicited eosinophilia in the airways. However, in a number of animal species, including monkey, rabbit, baboon and guinea pig, PAF does elicit airway eosinophilia. Using increasing doses of PAF, Sanjar and Colditz[15] showed that the number of eosinophils significantly increased in the bronchi after PAF challenge.

In summary, the non-H_1-antagonist effects of several second-generation antihistamines have been observed. These effects include inhibition of allergen-induced eosinophil, basophil, and neutrophil migration and inhibition of PAF-induced eosinophil accumulation in the skin by cetirizine.

PAF may contribute to the late reaction because of its point chemotactic activity for eosinophils; this effect of cetirizine may be from inhibition of both the late-phase allergic response and the effects of PAF in the skin. PAF is released from mast cells and is a potent chemotactic agent for eosinophils. For this reason, it may provide a link between the immediate and the late allergic reactions. The ability of cetirizine and possibly other second-generation antihistamines to inhibit these responses at usual therapeutic doses may be useful in investigating the late reaction.

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Commentary and discussion: Inhibition of mediator release

DETERMINING AN ANTIHISTAMINE'S MAST CELL–STABILIZING PROPERTY

Dr. Simons. The central question that we hope to address in this discussion is, "What is the clinical importance of the inhibition of mediator release by antihistamines?" What other key questions does the panel think we should address?

Dr. Kaliner. Another important question is whether H_1 antihistamines have a mast cell–stabilizing property. There is no doubt that the primary measurable event that occurs in rhinitis after mast cells are activated is vascular permeability. Because vascular permeability is one of the major physiologic responses to mast cell degranulation and is largely—albeit not exclusively—mediated by histamine, a good antihistamine will control that response.

Dr. Simons. The most potent antihistamines can almost abolish it completely.

Dr. Kaliner. Yes, depending on the dose and all of the other parameters involved. My question is then, how do you interpret the mast cell–stabilizing capacity of an agent if the primary event that agent affects is the event that allows you to measure the mast cell mediators?

If you review all of the data on mediator release, it can be confusing. Some studies show reductions in leukotrienes but not in prostaglandin D_2 or histamine; others show reductions in histamine but not in prostaglandin D_2 or leukotrienes; and others show consistent reductions in vascular permeability but not exclusive or total reductions.

Dr. Simons. The results vary even with the same drug. Depending on dose, duration of treatment, and end-organ studied, levels of mediators may or may not be decreased.

Dr. Kaliner. That is right depending on the study, but one thing is still obvious—that all effective antihistamines clearly block the primary physiologic event. However, after hearing all the data presented, I was less than positive about the mast cell–stabilizing property of these agents. Dr. Naclerio, your data in nasal lavage studies are the best, no question about it. However, even in your studies, when we looked at histamine reductions, we were talking about reductions from 4.5 to 3.5 or 2.5 ng/ml. The data from our laboratory show the same reduction. I am not certain that the difference between 4.5 and 2.5 ng/ml of nasal washings is a significant change.

My point is that we all acknowledge the flexibilities in these measurements. The whole concept of mast cell stabilization is based on them; yet they seem somewhat contradictory from study to study, and they are small changes in a very flexible parameter. Based on that type of evidence, how can we conclude whether terfenadine or any of the H_1 antihistamines is or is not a mast cell stabilizer?

Dr. Naclerio. To try to answer your question, I will stay with the data from my laboratory. One of the factors that has always been important in interpreting these studies is the *pattern* of response. You also look at the patterns of mediators. Why does one go up and another go down? That is where the strengths are in the lavage studies. In our studies of histamine release, I believed the data the first time we did the study. When we repeated the study in another group of subjects, we found the same effects in histamine release. Even though that decrease may be small, it is statistically significant and reproducible.

There is another important question we must answer—the question that Dr. Simons already raised: Does the statistical change in the model, which I believe is true, translate into clinical benefit? I do not

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