

The antiallergic effects of antihistamines (H₁-receptor antagonists)

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Most first-generation and second-generation H₁-receptor antagonists have readily demonstrable antiallergic effects in vitro, although high concentrations of some of the medications are required to inhibit mediator secretion from mast cells or basophils. These antiallergic effects can also be seen in vivo in skin, nasal, lung, and ocular challenge studies. Some H₁-receptor antagonists appear to have an antiallergic effect in one organ but not in another. In many in vivo studies, doses of H₁-receptor antagonists three or more times higher than those required for H₁ blockade must be given to achieve the antiallergic effect. It would be premature to attempt to reclassify the H₁ antagonists according to their antiallergic properties because these properties have not been investigated fully and their relative contribution to the overall therapeutic effectiveness of each H₁ receptor antagonist is unknown. (J ALLERGY CLIN IMMUNOL 1992;90:705-15.)

Key words: Allergic rhinitis, antihistamines, basophils, bronchoconstriction, mast cells, mediator release

H₁-receptor antagonists, which were introduced into clinical medicine more than five decades ago,¹ act principally by pharmacologic or competitive antagonism of histamine at H₁ receptors located in vasculature, airway smooth muscle, and neural tissues. The binding of H₁ antagonists to the histamine receptor does not produce any response, and for most H₁ antagonists binding is readily reversible. However, some of the second-generation H₁-receptor antagonists, such as astemizole, are not easily displaced from the receptor site, and their effects are not readily reversible on washout of the antagonist.²⁻⁴ Many of the newer H₁-receptor antagonists have a high degree of specificity for the H₁ receptor and are superb functional antagonists of histamine.²⁻⁴

The antiallergic effects of the H₁-receptor antagonists, although not a newly discovered phenomenon, have recently become a subject of considerable interest.⁵ There have even been suggestions that H₁-receptor antagonists should be reclassified according to their antiallergic properties.

In this article, selected in vitro and in vivo studies of the antiallergic effects of H₁-receptor antagonists

Abbreviations used

Con A: Concanavalin A
LTC₄: Leukotriene C₄
PGD₂: Prostaglandin D₂

are reviewed, with the emphasis on studies performed on human mast cells and basophils and studies performed in patients with allergic disorders.

IN VITRO STUDIES

First-generation H₁-receptor antagonists

In 1953 Arunlakshana⁶ was the first investigator to show that the antihistamine antazoline could both inhibit anaphylactic histamine release and act as a histamine liberator. This phenomenon was later extensively studied by Mota and Da Silva,⁷ who in 1960 reported that antihistamines such as mepyramine and diphenhydramine inhibited compound 48/80— or antigen-induced histamine release from guinea pig and rat mast cells. At very high concentrations, these antihistamines also caused histamine release, probably by way of a nonspecific cytolytic effect caused by micelle formation of the medication with cell membrane components.^{5,7}

In 1975 Lichtenstein and Gillespie⁸ reported that antigen-induced IgE-mediated release of histamine from human basophils was inhibited at 0.1 mmol concentrations by H₁ antagonists such as diphenhy-

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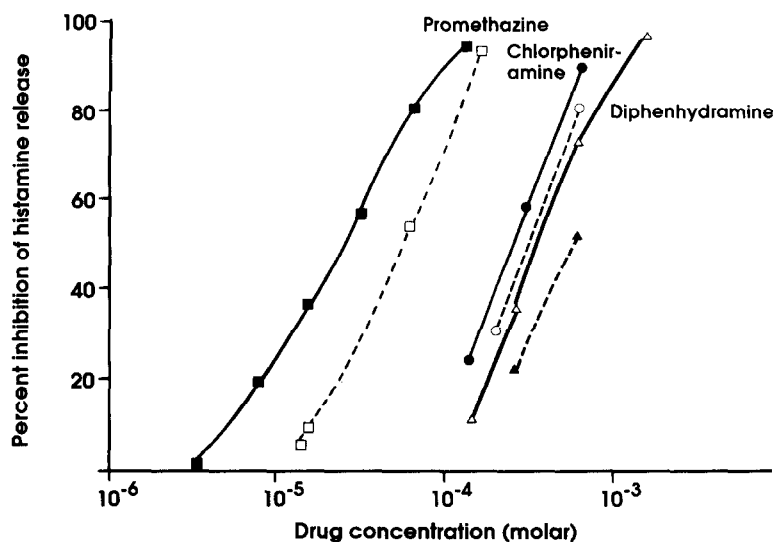


FIG. 1. Inhibition of antigen-induced histamine release from human leukocytes in vitro by H_1 -receptor antagonists. Leukocytes were added to tubes containing a concentration of antigen E sufficient to cause control histamine release of 70% to 80%. The reaction proceeded for 60 minutes at 37° C. Inhibition was calculated as follows: (histamine release in control tubes minus histamine release in antihistamine-containing tubes) divided by (histamine release from control tubes) times 100. Similar open and closed symbols represent different experiments with the same antihistamines. (From Lichtenstein LM, Gillespie E. The effects of the H_1 and H_2 antihistamines on "allergic" histamine release and its inhibition by histamine. *J Pharmacol Exp Ther* 1975;192:441-50. Copyright 1975 by the American Society for Pharmacology and Experimental Therapeutics.)

dramine and azatadine and enhanced by these medications at 1 mmol concentrations (Fig. 1). These investigators reported that the phenothiazine antihistamines were 10- to 30-fold more potent inhibitors than other H_1 antagonists. The mechanism of the inhibition was unknown, but it was not due to partial agonist activity, because the H_1 antagonists caused a significant fall in cyclic adenosine monophosphate levels. The potency of H_1 antagonists in producing the effects on histamine release did not appear to be correlated with their histamine H_1 -receptor-blocking activity.⁸

In 1980 Church and Gradidge,⁹ who studied human lung in vitro, reported that H_1 antagonists such as oxatomide, chlorpheniramine, ketotifen, promethazine, diphenhydramine, cyclizine, and mepyramine, as well as numerous other medications, inhibited anti-IgE-induced histamine release. Oxatomide, the most potent of these medications, was effective at nanomolar concentrations. It had approximately the same antiallergic potency as albuterol, and was 20,000 times more effective than cromolyn had been in previous similar studies by the same authors. The H_1 antagonists had a biphasic effect (Fig. 2). At low concentrations dose-related inhibition of histamine release was observed, whereas at higher concentrations the H_1 antagonists liberated histamine even in the ab-

sence of antigen. The authors speculated that mast cell stabilization played an important role in the antiallergic activity of these medications. The potency of the medications as histamine release inhibitors did not relate to their potency as histamine liberators. Also, no correlation existed between the antiallergic activity of the H_1 antagonists and the histamine H_1 -receptor activity of these medications.⁹

Second-generation H_1 -receptor antagonists

Subsequently, numerous investigators have found that many second-generation H_1 -receptor antagonists have antiallergic effects in vitro.^{5, 10-22} The antiallergic effect has been best studied for terfenadine, loratadine, cetirizine, azelastine, ketotifen, and oxatomide. In vitro these medications inhibit mediator release from rodent mast cells, human tissue mast cells, and peripheral blood basophils induced by immunologic stimuli such as antigen or anti-IgE or nonimmunologic stimuli such as compound 48/80, substance P, Con A, or calcium ionophore A23187. Their antiallergic effects vary, depending on the cell type and source, the concentration of the agonist or antagonist, and the mediator being quantitated.^{5, 10-22} Important evaluation criteria for in vitro studies are listed in Table I.

In vitro, terfenadine inhibits anti-IgE-induced histamine release from human basophils, and in high

TABLE I. Evaluation criteria for in vitro studies demonstrating the antiallergic properties of H_1 -receptor antagonists

Range of concentrations used encompasses those found in vivo after usual doses
Specific, sensitive mediator assay
Reproducibility of results

concentrations it inhibits calcium ionophore-induced histamine release from human basophils and LTC_4 release from human neutrophils.¹⁰ This study is discussed in depth later in these proceedings by Dr. Robert Townley.

At micromolar concentrations, loratadine inhibits the release of histamine from Con A- and calcium ionophore-stimulated rat peritoneal mast cells, which exhibit the properties of a connective tissue mast cell, and it inhibits the release of histamine and LTC_4 from Con A-stimulated MC9 cells, cloned murine mast cells that resemble mucosal mast cells. These effects occur at concentrations that are higher than the concentrations of loratadine that block contractile responses to histamine on guinea pig ileum. Loratadine also blocks antigen- and ionophore-induced leukotriene release from human lung in vitro.^{11, 12}

Astemizole inhibits histamine release from rat peritoneal mast cells but does not consistently inhibit antigen-induced histamine release from sensitized human lung tissue.¹³ Cetirizine inhibits anti-IgE-induced degranulation of human basophils, but this effect is less well documented than its effect on inhibiting generation of cytotoxic mediators from passively sensitized human platelets.¹⁴ Ketotifen is effective in inhibiting allergen-mediated histamine release from human cells in vitro.¹⁵ Azelastine inhibits histamine release from human basophils and LTC_4 and leukotriene D_4 release from human neutrophils but inhibits histamine release from lung mast cells only after prolonged preincubation.¹⁶⁻¹⁹

In some in vitro studies the concentrations of the H_1 -receptor antagonist used to suppress histamine release from mast cells and basophils are higher than concentrations achieved in vivo after ordinary doses of H_1 -receptor antagonists (Table I). Only a few studies of the antiallergic effects of H_1 -receptor antagonists have been performed to date with the H_1 -antagonist metabolites as well as with the parent compound (Fig. 3).²⁰

Many H_1 antagonists are lipophilic, cationic drugs. They can dissolve into the cell membrane, causing it to expand, stabilize, and become less permeable to ion fluxes (specifically sodium influx) and the consequent release of calcium from intracellular sites.

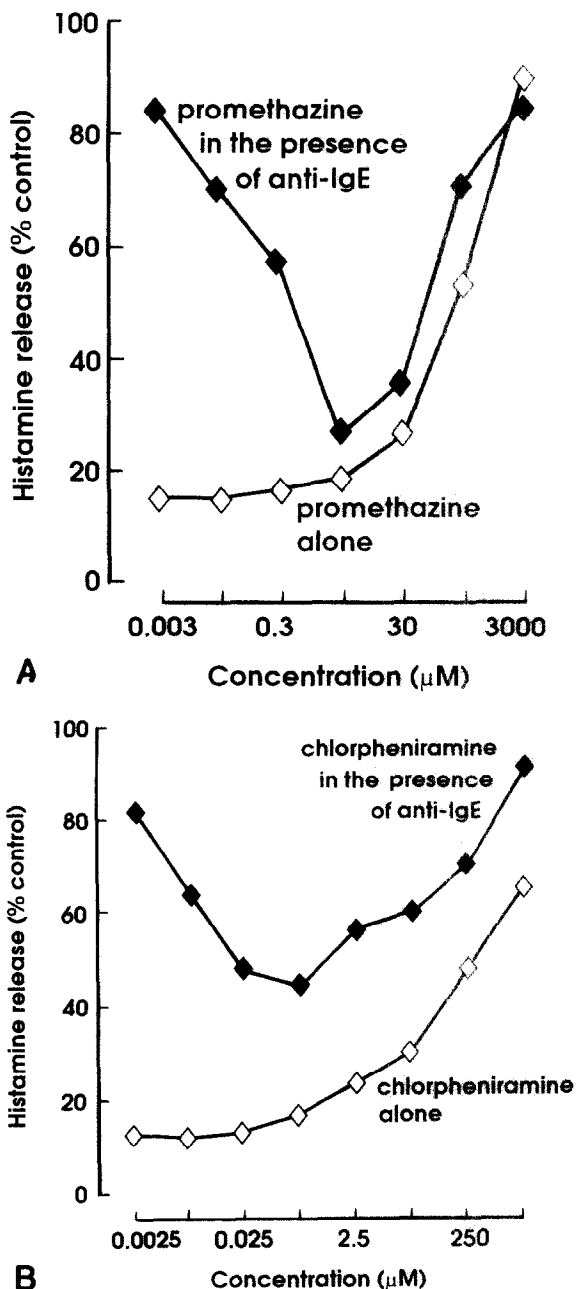


FIG. 2. Effects of **A**, promethazine and **B**, chlorpheniramine on anti-IgE-induced histamine release from human lung in vitro. Each point is the mean of the results of five experiments. Solid diamonds represent the H_1 antagonists in the presence of anti-IgE; open diamonds represent H_1 antagonists alone. (From Church MK, Gradidge CF. Inhibition of histamine release from human lung in vitro by antihistamines and related drugs. *Br J Pharmacol* 1980; 69:663-7.)

However, the correlation between lipophilicity of the H_1 antagonists and their inhibitory and cytotoxic properties at low and high concentrations, respectively, is imprecise.⁵

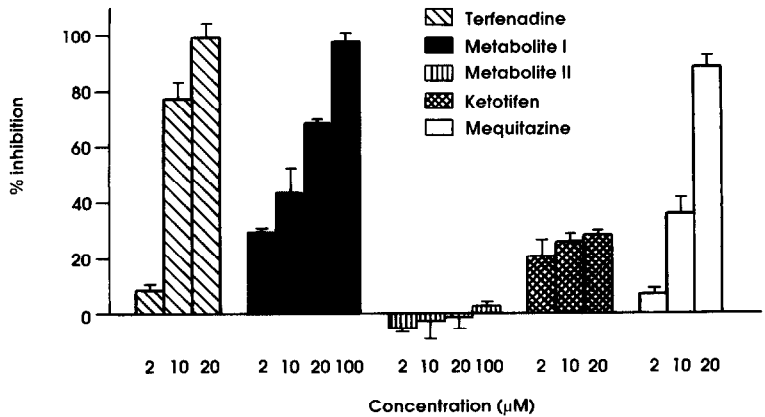


FIG. 3. Terfenadine and the active human carboxylic acid metabolite of terfenadine (terfenadine metabolite I), ketotifen, and mequitazine inhibit histamine release from rat peritoneal mast cells induced by 0.35 μg/ml of compound 48/80. In contrast, the *inactive* human metabolite of terfenadine (terfenadine metabolite II) does not have this inhibitory effect. Intracellular Ca²⁺ release was measured by loading cells with fluorescent Ca²⁺ indicator Quin 2 and exposing them to compound 48/80 in a Ca²⁺-free medium. Pretreatment with the H₁-receptor antagonist prevented the marked increase in Quin 2 fluorescence that occurred in untreated cells. This indicated that histamine release from intracellular Ca²⁺ stores had been inhibited. In other experiments theophylline and disodium cromoglycate had a similar inhibitory effect (not shown). (From Tasaka K, et al. Intracellular calcium release induced by histamine releasers and its inhibition by some antiallergic drugs. *Ann Allergy* 1986;56:464-9.)

TABLE II. Evaluation criteria for in vivo studies demonstrating the antiallergic properties of H₁-receptor antagonists

Double-blind
Placebo-controlled
Strict, uniform selection criteria for patients
Doses studied include manufacturers' recommended doses
Steady-state serum concentrations achieved
Appropriate washout between studies
Specific, sensitive mediator assay
Reproducible mediator measurements at baseline

H₁ antagonists may interfere with several stages of intracellular calcium ion utilization, for example, by producing voltage-sensitive calcium channel blockade, thus inhibiting calcium influx; by inhibiting calcium release from intracellular stores; or by inhibiting Ca²⁺ calmodulin-dependent phosphodiesterase or Ca²⁺ phospholipid-dependent protein kinase C (Fig. 4).^{21, 22} Although most studies of the mechanism of action of H₁-receptor antagonists in suppressing mediator release have focused to date on calcium ion utilization, probably because of the historical precedent of investigating the role of calcium and disodium cromoglycate in inhibition of mediator release, at H₁

antagonist concentrations usually achieved in vivo calcium antagonism is not likely to be the major mechanism of the antiallergic effects of H₁-receptor antagonists.²⁰⁻²²

IN VIVO STUDIES

In patients with allergic disorders, four models are currently used to study the effects of pharmacologic agents such as H₁-receptor antagonists in preventing the allergic response: a skin challenge model,²³⁻²⁷ a nasal antigen challenge model,²⁸⁻³⁵ a bronchial antigen challenge model,³⁶⁻⁴¹ and a less commonly used ocular antigen challenge model.⁴²⁻⁴⁴ In these models, patients are challenged out of season with an antigen to which they have been naturally sensitized. After challenge, symptoms and signs may be recorded, and mediators of inflammation and cells may be quantitated in recovered body fluids. Concomitantly, in some studies physiologic measurements, for example, change in nasal airway resistance, are made. The early allergic response, the late allergic response, and the rechallenge response can be investigated. Important evaluation criteria for in vivo studies, which demonstrate the antiallergic properties of H₁-receptor antagonists, are listed in Table II.

H₁-receptor antagonists appear to penetrate rapidly into body tissues, and H₁-receptor antagonist concen-

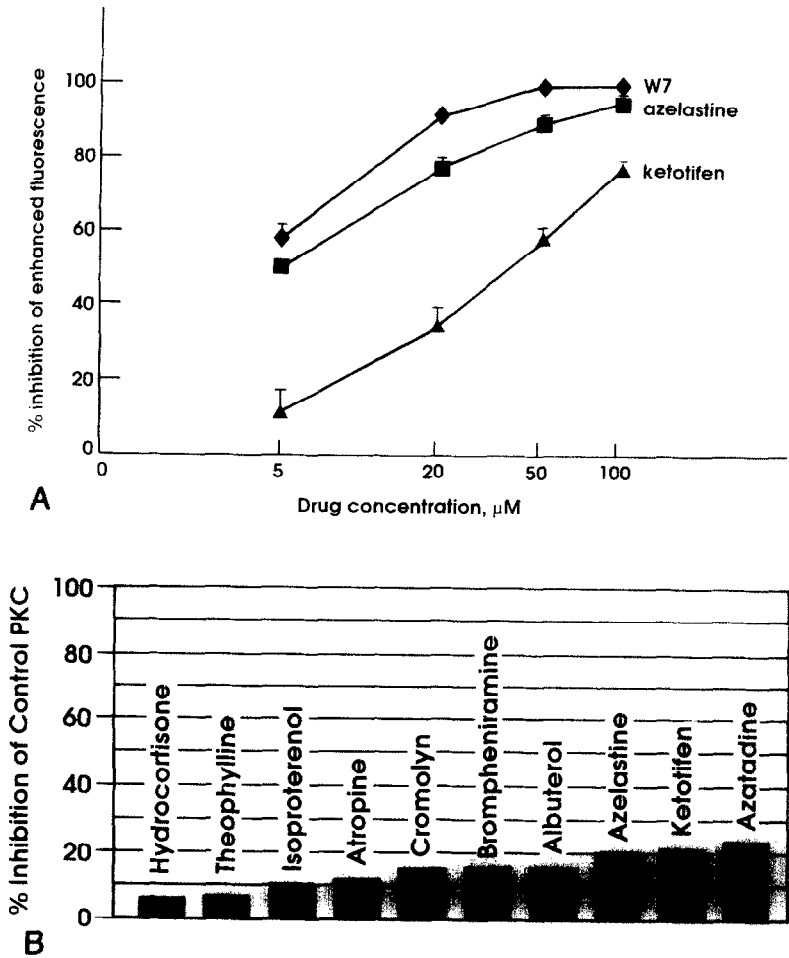


FIG. 4. A, Azelastine and W-7, a positive control for calmodulin reactivity, have a potent effect in reducing the enhanced relative fluorescence intensity of the 1-N-phenyl-naphthylamine calmodulin mixtures, as does ketotifen. **B,** Effect of various antiallergic medications on protein kinase C activity. None of the study medications at a 50 μmol concentration caused a marked inhibition of protein kinase C activity stimulated by diolein. Azelastine, ketotifen, and azatadine caused approximately 20% inhibition of the enzyme, a marginal effect in contrast to quercetin, a known inhibitor of protein kinase C, which caused approximately 80% inhibition of the enzyme (data not shown). (From Middleton E Jr, et al. The effect of azelastine and some other antiallergic drugs on calmodulin and protein kinase C. *Agents Actions* 1989;28:9-15.)

trations that can be achieved in target organs such as the skin are higher than serum H_1 -antagonist concentrations.⁴⁵ The manufacturers' recommended doses for H_1 -receptor antagonists are based on information obtained in histamine-receptor blockade studies. Higher doses of these agents are often required to produce an antiallergic effect compared with those required to produce H_1 blockade. Also, the temporal relationships of the antiallergic effects and the H_1 blockade are not necessarily identical. Selected studies of the antiallergic effects of H_1 -receptor antagonists in the skin and in the nose will be discussed.

Antigen challenge studies in the skin

In 1985 Ting et al.,²³ who used a modified heat/suction skin blister technique in the skin of ragweed-sensitive individuals, were the first to report the inhibitory effect of an H_1 antagonist on antigen-induced histamine release in vivo. These investigators found that 25 mg of oral hydroxyzine four times daily for 3 days significantly inhibited ragweed (1000 protein nitrogen units/ml)-induced ultrastructural evidence of mast cell granule exocytosis 10 minutes after challenge. It significantly inhibited in vivo histamine release 30 minutes after challenge (Fig. 5). In addi-

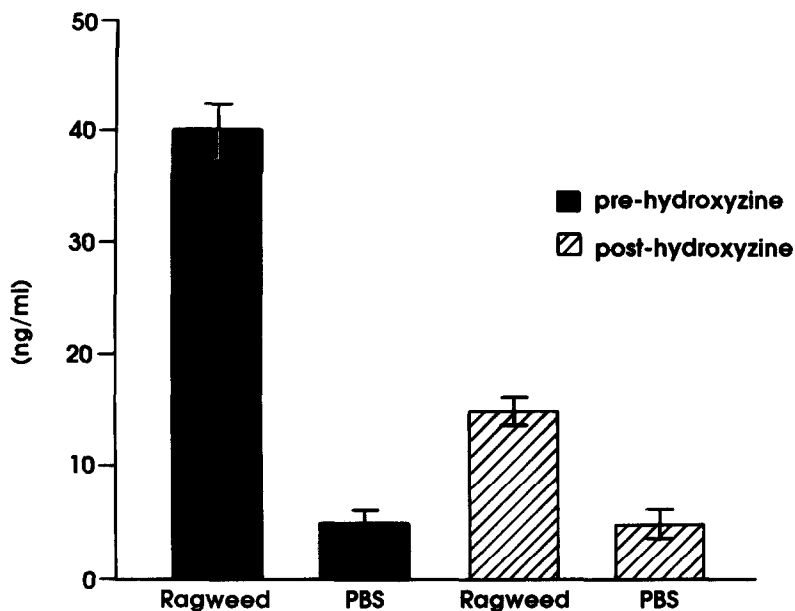


FIG. 5. Oral hydroxyzine, 25 mg four times daily, significantly inhibited ragweed antigen-induced ultrastructural changes of mast cells (not shown) and inhibited *in vivo* histamine release in the skin of ragweed-sensitive individuals. A modified heat/suction skin-blister technique was used. Histamine levels (mean $\pm$ SEM) in skin chamber fluids after 30 minutes incubation with ragweed are shown. *PBS*, Phosphate-buffered saline. (From Ting S, et al. Inhibitory effect of hydroxyzine on antigen-induced histamine release *in vivo*. *J ALLERGY CLIN IMMUNOL* 1985;75: 63-6.)

tion, it significantly reduced the size of wheals caused by intradermal injections of ragweed.

In a recent placebo-controlled, double-blind study in 15 patients with chronic urticaria and 10 normal volunteers, 100 mg of hydroxyzine daily for 28 days significantly relieved symptoms in the patients with chronic urticaria but actually *increased* compound 48/80-induced histamine release into skin blister fluid in these patients, although it decreased histamine release in normal control subjects (Fig. 6).²⁴ Terfenadine, 120 mg daily for 28 days, or placebo had no effect on the clinical response or on the histamine release profile in the patients with chronic urticaria, although terfenadine decreased histamine release in the normal control subjects.²⁴ In this study the compound 48/80 challenge in the skin blisters was made 90 minutes after the last H_1 antagonist or placebo dose.

Pretreatment with 20 mg of cetirizine daily for 4 days in a placebo-controlled, double-blind study was highly effective in 6 of 10 patients in inhibiting PGD_2 generation in a human skin chamber model, although it was ineffective in suppressing histamine release.²⁵ In another similarly designed study in which eight patients were given 10 mg of cetirizine twice daily for 5 days, pretreatment with cetirizine did not inhibit PGD_2 release at 30 minutes or at 6 or 24 hours and

did not inhibit histamine release at 30 minutes or 6 hours; however, it did inhibit histamine release at 24 hours²⁶ (Fig. 7). In both of these studies, cetirizine also significantly inhibited eosinophil influx.^{25,26}

In one small, uncontrolled study, 2 mg of ketotifen given twice daily for 1 month to patients with cold- or exercise-induced urticaria or dermographism inhibited the elevation of *plasma* histamine levels as well as the symptoms produced by relevant physical stimuli.²⁷

Antigen challenge studies in the nose

Histamine is the chemical mediator of inflammation of primary importance in patients with allergic rhinitis, as discussed by Dr. Martha White and Dr. Michael Kaliner in the first paper in these proceedings. Consequently, the antiallergic effect of histamine receptor antagonists in the nose is of considerable interest.

In the nasal challenge model, pretreatment with topical H_1 -receptor antagonists such as azatadine²⁸ prevents the symptoms of allergic rhinitis and inhibits mediator release. Pretreatment with topical levocabastine²⁹ also raises the threshold for the allergic response.

Pretreatment with all oral H_1 -receptor antagonists studied to date prevents nasal symptoms after in-

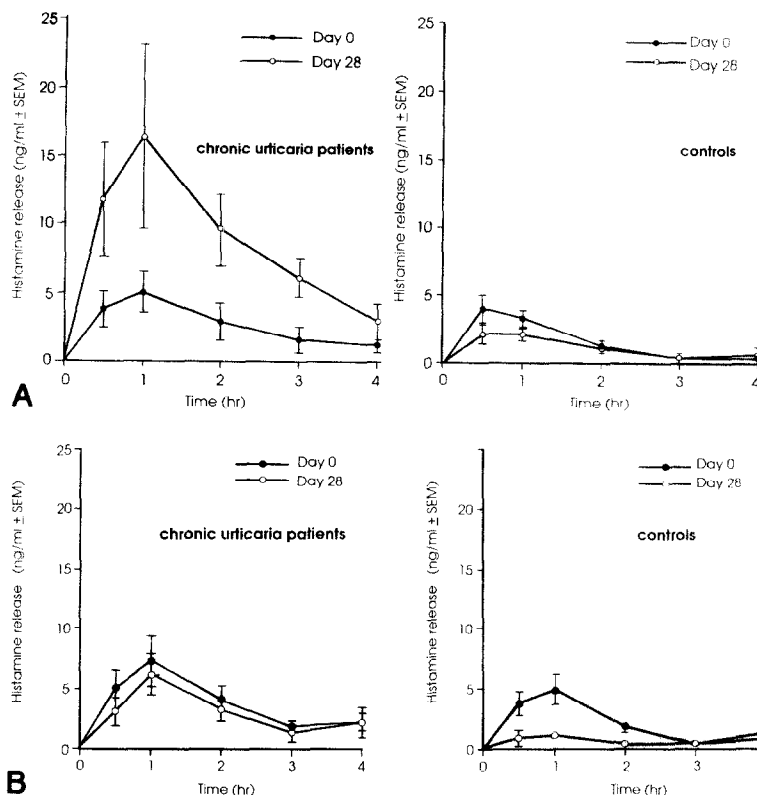


FIG. 6. Profile of histamine release in patients with chronic urticaria is shown before (day 0) and after (day 28) treatment with hydroxyzine, 100 mg per day, or terfenadine, 120 mg per day, or placebo, for 28 days. Effect of treatment on the clinical response and the profile of compound 48/80-induced histamine release during a 4-hour period was analyzed. **A,** In patients with chronic urticaria, treatment with hydroxyzine improved clinical symptoms but actually increased histamine release at 1 and 2 hours ($p < 0.05$) compared with baseline. In normal control subjects, the amount of histamine recovered 1 hour after challenge with compound 48/80 was lower than that of histamine released before treatment ($p < 0.01$). **B,** In patients with chronic urticaria, terfenadine had no effect on the clinical response or the profile of histamine release. In normal control subjects, the amount of histamine recovered 1 hour after challenge with compound 48/80 was lower than that of histamine released before treatment with terfenadine ($p < 0.01$). (From Brunet C, et al. Effects of H₁ antihistamine drug regimen on histamine release by nonlesional skin mast cells of patients with chronic urticaria. *J ALLERGY CLIN IMMUNOL* 1990;86:787-93.)

tranasal allergen challenge. Terfenadine^{30, 31} and loratadine,³¹ but not cetirizine,³² diphenhydramine,³³ or ketotifen,³⁴ also inhibit local mediator release after intranasal allergen challenge. A few of these studies will be discussed in detail.

In a placebo-controlled, double-blind crossover study in 12 patients with ragweed- or grass-induced allergic rhinitis, pretreatment with 60 or 300 mg of terfenadine twice daily for 1 week resulted in a significant decrease in nasal symptoms and of histamine, kinins, TAME-esterase, and albumin in nasal lavage fluid, in contrast to placebo treatment.³⁰ This study will be more extensively discussed by Dr. Robert Nacclerio later in these proceedings.

In another double-blind, crossover study that was not placebo-controlled, pretreatment with 60 mg of terfenadine twice daily or 10 mg of loratadine once daily for 1 week before intranasal challenge with orchard grass pollen in 14 patients who were highly allergic to orchard grass significantly increased the mean number of pollen grains required to produce symptoms compared with a control day.³¹ Ten of 14 patients had significant release of histamine on the control day, but only six patients had significant release of histamine after pretreatment with terfenadine ($p < 0.01$), and this release generally occurred at a higher dose than on the control day. Only one patient had a significant release of histamine after pretreat-

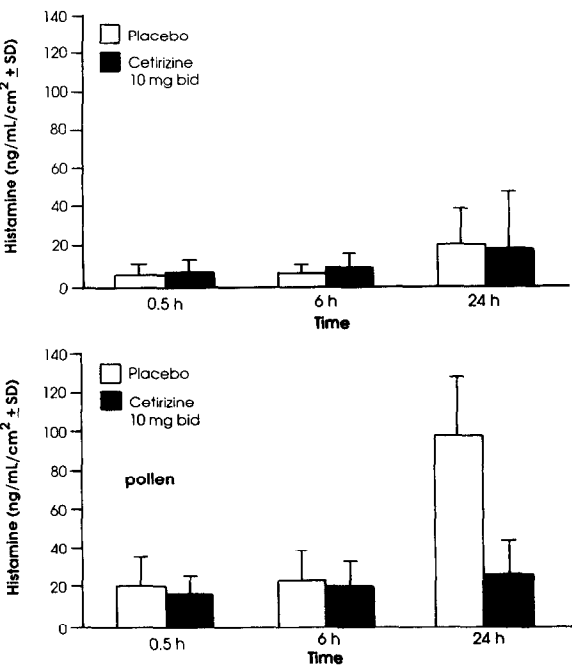


FIG. 7. In eight pollen-sensitive patients, the effect of 10 mg of cetirizine twice daily for 5 days versus placebo for 5 days is shown on pollen-induced histamine release in skin blister fluid at 30 minutes, 6 hours, and 24 hours. *Top panel* shows histamine release in control chambers filled with Hanks' balanced salt solution. *Bottom panel* shows histamine release induced by pollen. Decrease in histamine release after pollen challenge was significant at 24 hours in patients after pretreatment with cetirizine, in contrast with the amount of histamine released after pretreatment with placebo. Neither cetirizine nor placebo reduced PGD₂ release at 30 minutes, 6 hours, or 24 hours (not shown). (From Michel L, et al. Cetirizine effects on the cutaneous allergic reaction in humans. *ANN ALLERGY* 1990;65:512-6.)

ment with loratadine ($p < 0.00023$). Mean values of histamine in nasal secretions did not differ in nasal secretions at baseline, after lactose insufflation, after challenge with 50 grass pollen grains, and at the maximal release of histamine because of wide variations in baseline values (0.5 to 34.1 ng/ml). PGD₂ release occurred with a higher allergen dose after pretreatment with terfenadine or loratadine than on the control day. There was a significantly lower amount of PGD₂ in nasal secretions when the challenge was positive in patients treated with loratadine or terfenadine than the amount of PGD₂ on the control day (Fig. 8).

In a double-blind, placebo-controlled study of 10 patients with ragweed or grass allergy, 20 mg of cetirizine daily for 2 days was ineffective in inhibiting PGD₂ release or histamine release in the nasal challenge model, in contrast to the skin blister model.³² However, in the nasal challenge model, it suppressed

TABLE III. H₁-receptor antagonists decrease mediator release from mast cells and basophils

H ₁ -receptor antagonist	In vitro	Nasal model	Skin model
Terfenadine	✓	✓	—
Astemizole	✓	—	×
Loratadine	✓	✓	—
Cetirizine	✓	×	✓
Hydroxyzine	✓	—	±
Diphenhydramine	✓	×	—
Ketotifen	✓	×	✓
Azelastine	✓	—	—
Azadadine	✓	✓	—

✓, Yes; ×, no; ±, yes or no, depending on study; —, further information required.

LTC₄ release; the LTC₄ probably arose from a non-mast cell source, such as macrophages, epithelial cells, or eosinophils.

In 15 patients with allergic rhinitis, 5 days of pretreatment with 60 mg of terfenadine twice daily or 10 mg of cetirizine daily significantly decreased nonspecific nasal reactivity, which was measured as methacholine-induced nasal secretions. However, neither agent decreased nasal eosinophil infiltration 24 hours after antigen challenge.³⁵

Ketotifen was ineffective at inhibiting histamine release after nasal challenge with antigen.³⁴

Antigen challenge studies in the lower airways

Pretreatment with H₁-receptor antagonists, such as terfenadine, astemizole, loratadine, azelastine, and ketotifen, inhibits the early and late bronchoconstrictor responses to inhaled allergen in patients with asthma.³⁶⁻⁴¹ In a few of these studies, the effect of H₁-receptor antagonists on serum concentrations of mediators of inflammation has been measured. Ketotifen was ineffective at inhibiting the rise in serum neutrophil chemotactic factor concentrations after allergen challenge.³⁹ Neither astemizole⁴⁰ nor azelastine⁴¹ inhibited the elevation of plasma histamine concentrations after antigen challenge; however, the dose of azelastine used probably resulted in plasma azelastine concentrations about one tenth or one twentieth of those required to decrease mediator release in vitro.⁴¹

Clinical significance of the antiallergic effects of H₁-receptor antagonists

It is apparent from this brief review that some H₁-receptor antagonists seem to be more effective in suppressing mediator release in one model than in an-

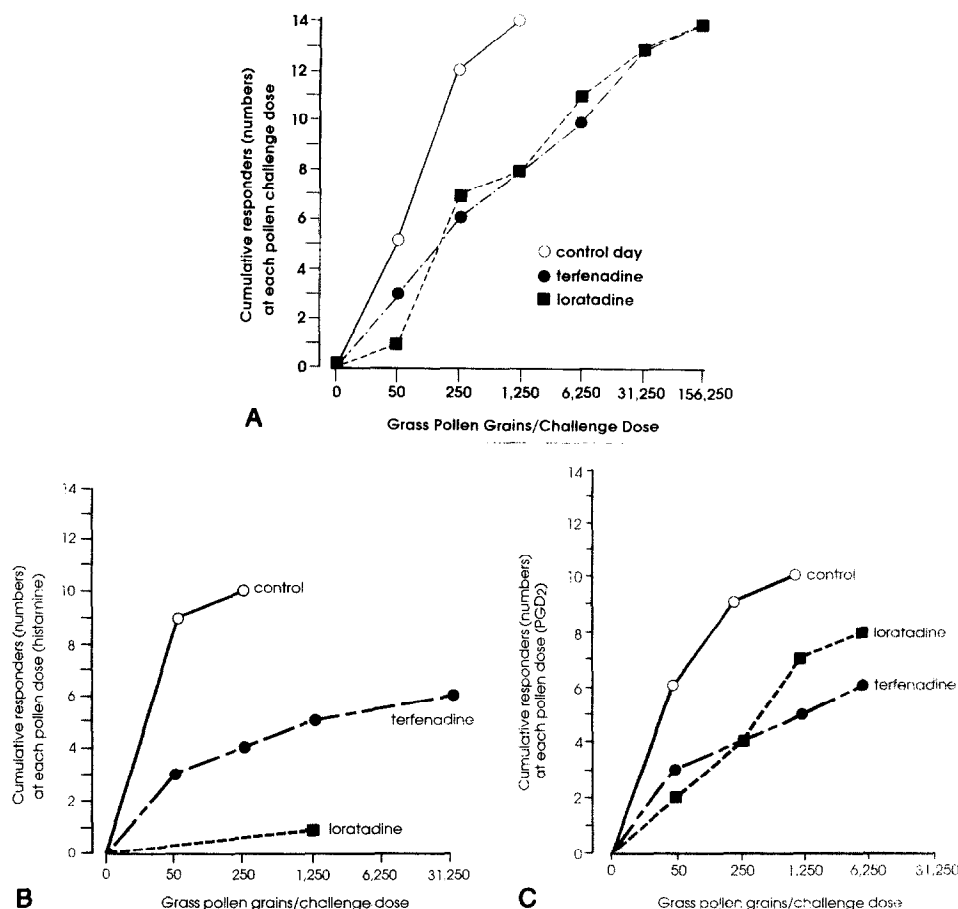


FIG. 8. Effect of 60 mg of terfenadine twice daily or 10 mg of loratadine once daily on the immediate allergic response of the upper airways to orchard-grass pollen challenge was studied in 14 highly allergic patients. Each medication was administered for 1 week before challenge. No placebo pretreatment was given. **A**, Cumulative numbers of patients responding with significant symptoms after orchard-grass pollen challenge. **B**, Cumulative numbers of patients with a significant rise (twice baseline level measured after lactose insufflation) in histamine in nasal secretions after orchard-grass pollen challenge. Only one patient had a significant release of histamine when treated with loratadine versus six after terfenadine treatment and 10 on the control day. **C**, Cumulative numbers of patients with a significant rise (twice baseline value) after lactose insufflation (in PGD₂) in nasal secretions after orchard-grass pollen challenge. PGD₂ release occurred at a higher allergen dose when patients were treated with loratadine or terfenadine than on the control day. (From Bousquet J, et al. Antiallergic activity of H₁ receptor antagonists assessed by nasal challenge. *J ALLERGY CLIN IMMUNOL* 1988;82: 881-7.)

other. For example, cetirizine and ketotifen seem to have a much more potent antiallergic effect in the skin than in the nose. Most H₁-receptor antagonists have been studied in only a few of the models (Table III), and comprehensive overviews of their antiallergic effects are not yet available.

These studies are time-consuming and difficult to perform; also, some published studies do not meet the criteria of excellence suggested in Table II. Comparison of the results of studies performed in different laboratories is difficult because of the different meth-

ods used. Some of the apparent discrepancies in the literature may reflect the different doses of H₁-receptor antagonists given, the varying duration of treatment, and the range of concentrations of H₁-receptor antagonists achieved in vivo, because it is obvious from numerous in vitro studies that the concentrations of some H₁-receptor antagonists required for an antiallergic effect may be rather high. Later in these proceedings, Dr. Robert Naclerio will present a definitive nasal challenge study that answers many of the current questions about the nasal challenge model.

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Inhibition of mediator release during the early reaction to antigen

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A nasal lavage model and a new filter paper disk model have been used to measure biologic and physiologic responses to antigen challenge in patients with allergic rhinitis. Pretreatment of subjects with cetirizine reduced the number of sneezes induced by antigen challenge but did not significantly reduce levels of histamine or prostaglandin D₂ in a double-blind, placebo-controlled trial with the lavage model. Pretreatment with 60 or 300 mg of terfenadine did significantly reduce levels of histamine, kinin, albumin, and TAME-esterase activity in a double-blind, placebo-controlled study with this model. Again with the nasal lavage model, a double-blind, placebo-controlled comparison of pretreatment with 60 mg of terfenadine or 10 mg of loratadine showed that both agents significantly reduced sneezing. Both drugs also lowered levels of antigen-induced histamine and TAME-esterase, but only terfenadine did so significantly. In a double-blind, placebo-controlled study, the new disk method showed that terfenadine reduced sneezing but not nasal congestion in eight patients with allergic rhinitis. Terfenadine significantly reduced the weight of nasal secretions on both sides of the nose and significantly reduced histamine on the ipsilateral side. (J ALLERGY CLIN IMMUNOL 1992;90:715-9.)

Key words: Allergic rhinitis, antigen, histamine, mast cell, cetirizine, loratadine, terfenadine

We have used a lavage technique for several years at Johns Hopkins to study the response to antigen challenge. In this nasal model a metered-dose inhaler is used to spray antigen into the subject's nose so that a reproducible dose can be delivered to the nasal mucosa. The response is monitored by nasal lavage. The subject closes off the nasopharynx; 10 ml of saline solution is then placed into the nasal cavity. After 10

Abbreviations used

H₁: Histamine type 1 receptor
PGD₂: Prostaglandin D₂
LTC₄: Leukotriene C₄
PNUs: Protein nitrogen units

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seconds, the subject brings forth secretions and saline solution into a plastic receptacle. The recovered fluids are then processed for the measurement of mediators.

When antigen is sprayed into the nasal mucosa, it stimulates nasal mast cells to release histamine, and that released histamine then stimulates nerves to cause