

Clinical comparison of histamine H₁-receptor antagonist drugs

Lawrence M. Du Buske, MD Fitchburg, Mass.

Nearly 40 million Americans have symptoms of upper respiratory allergies, making antihistamines among the most frequently used pharmacologic agents. Although there are mediators of allergic symptoms in addition to histamine, therapy for allergic rhinitis and urticaria has focused upon the use of antihistamines. The classic histamine H₁-receptor antagonists, however, are not selective for the H₁ site and produce a variety of dopaminergic, serotonergic, and cholinergic responses leading to considerable adverse effects in the central nervous system consequent to both their pharmacologic nonselectivity and their ability to penetrate the blood-brain barrier readily. The second-generation antihistamines were a major advance in the therapy of allergic rhinitis, because they do not penetrate the blood-brain barrier as rapidly and are also designed for greater specificity at H₁-receptor. Given their greater selectivity for the H₁-receptor, they cause fewer undesirable central nervous system actions, whereas their efficacy is similar to that of the classic antihistamines used in the treatment of allergic rhinitis. Selecting among these antihistamines for the treatment of allergic rhinitis has focused on their pharmacokinetics and adverse effect profiles. The potential cardiotoxic effects of some antihistamines when their metabolism is inhibited requires caution in prescribing these agents. The antiallergic and antiasthmatic effects of several newer antihistamines are being explored. For the clinician, making the therapeutic decision among H₁-receptor antagonists requires a comprehensive knowledge of their diverse effects. (J Allergy Clin Immunol 1996;98:S307-18.)

Key words: H₁-receptor antagonists, allergy therapy, antihistamines

In the five decades since clinically useful histamine₁ (H₁)-antagonists were introduced to medicine, these therapeutic agents have emerged as one of the most widely used classes of drugs in the world.¹ The benefits of antihistamines have become apparent in controlling allergic rhinitis, a condition that affects nearly 22% of all Americans² and in controlling chronic urticaria, atopic dermatitis, and other allergic disorders. These valuable drugs block activation of the H₁-receptors, which can stimulate sensory nerves and increase vascular permeability and mucus production. Blocking H₁-receptors prevents the histamine contribution to the symptoms of allergic rhinitis: nasal itching and congestion, sneezing, rhinorrhea, and ocular irritation.

Although similar in some actions, H₁-receptor antihistamines are pharmacokinetically and pharmacodynamically diverse (Table I). This drug class encompasses a group of chemically different compounds with the similar pharmacologic ability to competitively antagonize

Abbreviations used

CNS:	Central nervous system
H ₁ :	Histamine H ₁
H ₂ :	Histamine H ₂
H ₃ :	Histamine H ₃
ICAM-1:	Intracellular adhesion molecule-1
LPR:	Late-phase response
LTB ₄ :	Leukotriene B ₄
LTC ₄ :	Leukotriene C ₄
PGD ₂ :	Prostaglandin D ₂

histamine at its receptors. They have a similar core moiety, but the radicals or side chains adjoining the core determine their various pharmacokinetic properties (absorption, distribution, and elimination). Most H₁-antagonists are rapidly absorbed and provide symptom relief within 30 minutes. Once-daily (or at most twice-daily) dosing of second-generation antihistamines is made possible by the persistence of the biologic activity of these medications for a time significantly exceeding their serum half-life.

From the Immunology Research Institute of New England and Harvard Medical School.

Reprint requests: Lawrence M. Du Buske, MD, IRINE, 955 South St., Fitchburg, MA 01420.

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TABLE I. Pharmacokinetics of H₁-receptor antagonists

Drug	B-phase serum elimination half-life	Suppression of wheal response
Chlorpheniramine	24.2 (11.0*)	24 hr
Brompheniramine	24.9	3-9 hr
Triprolidine	2.1	—
Hydroxyzine	20.0 (7.1*)	2-36
Cetirizine	7.4 (7.0*)	24 hr
Loratadine	11.0	24 hr
Terfenadine†	4.5 (2.0*)	12-24 hr
Astemizole	10 days§	≤8 weeks

*Serum elimination half-life value in children.

†Including terfenadine metabolite I.

§Including its major metabolite.

Data from Simons EF. *J Allergy Clin Immunol.* 1989;84:845-61.

VARIETY OF ANTIHISTAMINES

Clinically useful antihistamines were first developed in the late 1930s and 1940s. Because these classic H₁-receptor antagonists are not selective for the H₁-receptor site, they induce a variety of dopaminergic, serotonergic, and cholinergic responses. First-generation antihistamines contain aromatic rings and alkyl substitutes that make them lipophilic, explaining their ability to cross the blood-brain barrier rapidly.³ In the brain, these antihistamines inhibit histamine N-methyltransferase or block central histaminergic receptors. These drugs induce considerable adverse effects in the central nervous system (CNS) as a result of their pharmacologic nonselectivity for the H₁-receptor and ability to penetrate the blood-brain barrier easily. Four types of adverse CNS effects can emerge with nonselective agents: stimulatory, neuropsychiatric, peripheral, or depressive.³

In the 1980s, second-generation antihistamines were formulated, largely by synthesis of compounds with a lower lipid solubility due to a charged side chain. This major breakthrough achieved histamine-receptor blockade without dramatic CNS effects. Some of these compounds were also designed for greater specificity at H₁-receptors. Terfenadine was the first second-generation antihistamine approved by the Food and Drug Administration. Cetirizine and fexofenadine are the most recently approved antihistamines.

The newer agents have fewer adverse effects when compared with older, first-generation agents. However, most studies have found them to be as effective as the first-generation drugs as therapy for allergic rhinitis.

Certain tricyclic antidepressant agents—doxepin in particular, with its potent H₁-receptor and histamine-2 (H₂)-receptor antagonist properties—are potentially useful therapy for diseases such as chronic urticaria. The effects of the tricyclic antidepressants are long-lasting and H₁-induced responses in the skin are suppressed for as long as 2 weeks after discontinuation of the therapy.

Doxepin was found to be among the most potent H₁-receptor antagonists. Doxepin has unusual pharmacologic ability and was used as a treatment for peptic ulcer disease when first produced. Of note, terfenadine was originally synthesized as part of an effort to find new antipsychotic agents.⁴

THREE SUBTYPES OF HISTAMINE RECEPTORS

Since histamine was discovered as a mediator of the allergic response early in this century, considerable information has emerged about the complexity of the allergic response and the cascade of mediators involved.

Histamine is found in all body tissues, although its highest concentrations are found in the lungs, mast cells, and basophils. Upon exposure of a sensitized host to a sensitizing antigen, the bridging of at least two IgE molecules to these cells occurs, activating the release of histamine and other inflammatory mediators. At the H₁-receptor found on nerve endings, smooth muscles, and glandular cells, histamine induces reactions such as a wheal and flare in the skin; bronchial constriction and mucus secretion in the lungs; congestion and irritation in the nose; and edema and hypotension during generalized anaphylaxis.

In addition to H₁-receptors, two other subtypes of histamine receptors have been identified. In the late 1970s, recognition of the gastrointestinal effects of H₂-receptors led to the development of H₂-receptor antagonists for the treatment of duodenal ulcer and reflux esophagitis, conditions associated with gastric hyperactivity. The effects of H₂-antagonists on allergic response are less well defined although some have been reported to be effective in the treatment of chronic urticaria and acute anaphylaxis; to have an effect on bronchial smooth-muscle tone and mucus secretion; and to increase cyclic adenosine monophosphate.⁵

The most recently identified histamine subtype is the histamine-3 (H₃) group. H₃-receptors may be important modulators of histamine synthesis and release in cerebral neurons in the CNS. They may also decrease histamine release from mast cells and release of proinflammatory tachykinins from unmyelinated C-fibers in airways. Therefore they may have a role in the modulation of inflammatory allergic airway disease.⁶ The H₃-receptor has been proposed to function as an autoreceptor for cholinergic neurotransmission at the level of the autonomic ganglia in the airways.⁷

ANTIHISTAMINES AND THE CLINICAL ALLERGIC REACTION

The allergic response occurs in two phases: the immediate- or early-phase response and the late-phase reaction (LPR). Clinically, the immediate development of the allergic reaction—sneezing, watery nasal secretions, and itching of the nose and eyes—occurs within 30 minutes when the person with sensitivity encounters an allergen. If a cat-sensitive person enters a room in which a cat is present, the early-phase allergic response may occur immediately. If this person is exposed to cats for a

longer period, more intense symptoms may develop, often in conjunction with nasal congestion and sinus headaches. Immediate symptoms upon allergen exposure can be followed from 6 to 48 hours later by an immunologic LPR to the allergen. The degree and duration of allergen exposure is critical in determining the intensity of the response. Short, limited exposures often produce an isolated early-phase response whereas longer, more intense exposures can produce both early-phase responses and LPRs or rarely, isolated LPRs.

In the early-phase response, mast cells are activated upon cross-linking of the membrane-bound IgE by a specific allergen. This process results in the immediate release by mast cells of preformed mediators of allergic inflammation that are stored within the secretory granules and the production of newly formed lipid-derived mediators, including those generated by metabolism of arachidonic acid liberated from the mast cell. In addition, cytokine synthesis and release occurs consequent to mast-cell activation. Histamine exists in the mast-cell secretory granules as do tryptase and chymase (serine proteases) and carboxypeptidase (an enzyme). Membrane-bound arachidonic acid is liberated from phospholipid in several well-described pathways. Arachidonic acid metabolites include leukotrienes (leukotriene B₄ [LTB₄] and leukotriene C₄ [LTC₄]) and prostaglandin D₂ (PGD₂). The phospholipid from which arachidonic acid has been liberated may be metabolized to form platelet-activating factor (PAF), which is formed in, but not released by, mast cells.

Histamine is one of several molecules that can induce significant symptoms of the immediate allergic response, but it is clearly not the sole mediator of allergy. During immediate hypersensitivity reactions, histamine is released from mast cells, reaching tissue concentrations of 10⁻⁵ to 10⁻³ mol/L.¹

The relative contribution of leukotrienes, prostaglandins, and histamines in the production of the allergic response may be dependent in part on the ultimate end-organ involved in the response. In the lung, for instance, antihistamines produce only a transient 10% to 15% increase in FEV₁, which lasts ≤2 hours, whereas leukotriene antagonists produce a greater, more sustained increase in FEV₁ after administration. Histamine, LTC₄, and PGD₂ have many parallel actions, including induction of vasodilatation, vascular leakage, and bronchoconstriction. However, LTC₄ is approximately 1000-fold more potent as a bronchoconstrictor than histamine.

The differing effects of histamine, leukotrienes, and prostaglandins in the allergic response may also be related to their relative concentration during these responses; however, differences in potency based on the relative effect per mole of mediator must be interpreted with caution because some mediators formed in minute quantities may be metabolized rapidly after release. The production of histamine and arachidonic acid metabolites in the allergic response may also be related to the mast-cell subtypes found within the responding organ,

that is, the skin, submucosa, intestine, lung, and nose. Therefore the greater efficacy of antihistamines in allergic rhinitis compared with allergic asthma may be associated with the relative production of mediators by mast cells and other inflammatory cells in the nose and lung.

During the early-phase allergic response, relevant chemotactic factors include LTB₄, eosinophil chemotactic factor of anaphylaxis, and neutrophil chemotactic factors. Ultimately, cytokines that up-regulate inflammatory cell function and enhance inflammatory cell migration are also produced not only by mast cells but also by eosinophils, basophils, and lymphocytes, which are recruited consequent to mast-cell activation.

Patients may report symptoms of asthma or chronic refractory rhinitis associated with congestion that reflect the allergic LPR. The LPR occurs several hours after allergen exposure and is associated with an influx of eosinophils, neutrophils, basophils, and lymphocytes. Eosinophils are believed to be the primary cell involved in the LPR. Upon activation, eosinophils become hypodense and release granule-derived mediators of inflammation, including major basic protein and eosinophil cationic protein; eosinophil-derived neurotoxin; and lipid-derived mediators of inflammation, including leukotrienes. Neutrophils probably play a lesser role in the production of the LPR but also release significant amount of LTB₄, superoxide, and proteases that may enhance the LPR.

The increased levels of histamine noted during the LPR are not associated with similar increased levels of PGD₂.⁸ This observation suggests that mast cells, which release both histamine and PGD₂ in parallel upon activation, are less important than basophils during the LPR because basophils produce histamine in the absence of PGD₂ production.

THE EFFICACY OF ANTIHISTAMINES

The effects of antihistamines on allergic responses are largely related to competitive inhibition of H₁-receptors and vary throughout the body. In the lungs, histamine induces bronchoconstriction, and increases mucus production, with the end result being the clinical signs and symptoms of asthma; in the skin, vasodilatation and vascular leakage produce symptoms of typical urticaria; in the nose, vasodilatation and vascular leakage produce the typical watery discharge and mucous hypersecretion of allergic rhinitis; and hypotension, edema, and generalized erythema are characteristic of generalized anaphylaxis, a reaction including vasodilatation and vascular leakage.

Antihistamines modify the clinical responses seen during early-phase reactions, in which the role of histamine is more clearly defined than it is in the LPR. Depending on the dose, some H₁-antagonists may decrease the release of histamine from mast cells or isolated basophils in vitro and, in addition, block the effects of histamine. In immediate allergic responses, antihistamines have varying effects on other aspects of allergic

responses mediated by leukotrienes or prostaglandins. At least *in vitro*, release of some mediators from basophils and mast cells may be modulated to some degree by H_1 -antagonists. *In vivo*, some H_1 -antagonists may inhibit mediator release more effectively in one organ than in others.

Because the role of histamine in producing early-phase inflammation appears to be end-organ dependent and because the effects of histamine are complemented by the effects of leukotrienes and prostaglandins, the efficacy of antihistamine therapy is probably dependent on the site of the allergic response and the contribution of histamine to the response in that site. The redundant effects of mediators make it impossible for an antagonist of one mediator to be effective in alleviating all signs and symptoms of allergic disease. Furthermore, the maximum benefit from antihistamines is achieved with prophylactic treatment, before exposure to the allergen, because antihistamines are less effective in alleviating symptoms of the immediate allergic response once it is underway. They are most effective when they are occupying the H_1 -receptor site before histamine is released.

Signs and symptoms that are clinically related to the LPR, such as nasal congestion and sinus headaches, respond less well to traditional antihistamine treatment and often require the addition of a decongestant for significant clinical benefit. The most effective modulation of LPRs requires use of corticosteroids, including inhaled corticosteroids for allergic rhinitis. When the efficacy of inhaled nasal corticosteroids has been compared with either terfenadine or astemizole, the inhaled nasal steroids have demonstrated superior clinical efficacy in the relief of symptoms related to rhinitis, including nasal congestion.

JUDGING THE ALLERGIC RESPONSE THROUGH WHEEL AND FLARE REACTIONS

Antihistamine potency varies, as measured by the suppression of histamine-induced wheal by a single dose of medication. This response correlates with relief of symptoms of allergic rhinitis.^{9,10} The histamine-induced wheal-and-flare response is inhibited by all H_1 -antagonists, but they differ in the strength of the effect, time to peak effect, and duration of the effect. H_1 -receptor activation is necessary to demonstrate allergic reactivity in the allergen skin test. The characteristic wheal-and-flare response to an allergen appears to be dependent on histamine release from allergen-activated mast cells.

Analyzing the inhibition of the wheal-and-flare reaction induced by histamine or allergens is a standardized biologic test of the action of antihistamines. Dose-response relations can be compared with this test. The effect of these medications can persist even when plasma concentrations are undetectable, either because active metabolites are present or because the ratio of tissue to plasma concentration is high.¹¹ In fact, the duration of action of antihistamines on inhibition of sneezing, rhi-

norrrhea, and itching and on the wheal-and-flare response persists beyond the plasma half-life. The clinical duration of action for many H_1 -antagonists is approximately 24 hours, allowing for once-daily dosing of most of these drugs.¹² Astemizole, doxepin, and tricyclic antidepressants, among other agents, affect responses in the skin for weeks to months after discontinuation of therapy.

In single-dose evaluations, cetirizine is among the most potent of antihistamines. In single-dose studies of the histamine-induced wheal, cetirizine had greater activity than clemastine, hydroxyzine, loratadine, astemizole, mepyramine, and terfenadine.¹³ In addition to its effects on H_1 -receptors, cetirizine appears to decrease the levels of LTC_4 in nasal secretions, perhaps in relation to effects on eosinophil migration, and may have multiple activities on the pathophysiologic basis of the acute allergic response.¹⁴ Cetirizine is capable of decreasing intracellular adhesion molecule-1 (ICAM-1) expression on endothelial cells, thereby inhibiting inflammatory cell migration to the site of allergic inflammation.¹⁵ With time, there is no loss of efficacy in cetirizine's ability to suppress histamine-induced responses in the skin.¹⁶

COMPARING ADVERSE EFFECTS

Classic H_1 antagonists

Because most older H_1 antagonists have relatively similar potencies in competing for histamine-receptor sites, the clinical usefulness of these drugs is often judged on the adverse effect profile, including the potential for drug interactions. The first-generation antihistamines include triprolidine, diphenhydramine, chlorpheniramine, and hydroxyzine. Because the classic H_1 -receptor antagonists are not selective for the H_1 site and cross the blood-brain barrier, they induce a variety of dopaminergic, serotonergic, and cholinergic responses.¹⁷

There are four types of adverse reactions¹⁸:

1. Stimulatory reactions include appetite stimulation, muscle spasms, seizures, and the anticholinergic reactions of insomnia, nervousness, irritability, tremor, and tachycardia.
2. Neuropsychiatric reactions include anxiety, confusion, depression, and, rarely, hallucinations and psychosis.
3. Peripheral neurologic effects due to cholinergic blockade are dilated pupils, blurred vision, dry mouth, urinary retention, constipation, and impotence. Rare reactions include paresthesias and paralysis.
4. Depressive reactions include sedation, drowsiness, and lowered alertness and cognitive ability. An important consequence of this action is impairment of driving ability. The somnolent effects of diphenhydramine hydrochloride are so pronounced that it is now being used as nonprescription sleeping aid.

Antihistamine overdose has been linked to coma; stimulatory CNS effects such as seizures, dyskinesia, or dystonia; and neuropsychiatric effects such as hallucinations or psychosis.^{19, 20} Rarely, ataxia, delirium, and narcolepsy are also seen.

Elderly persons taking classic antihistamines have the greatest risk of side effects. Clinicians exploring changes in mental status in elderly patients should inquire about antihistamine use, because these changes can be drug-related effects. Patients who take these drugs for long periods may be unaware of the effects of impaired judgment and relative mental inefficiency in performance.

Clinically, long-term therapy with first-generation antihistamines such as chlorpheniramine appears to be less efficacious over a period of weeks. This phenomenon has led to the question of whether drug resistance or sub-sensitivity has developed in patients who are treated for several weeks with this type of agent. In a study²¹ of patients taking chlorpheniramine for 3 weeks, the suppression of skin-test responses to histamine was correlated with serum chlorpheniramine levels achieved after 3 days and after 3 weeks of therapy. At both time points, similar serum levels of chlorpheniramine blocked histamine-induced wheal responses to a similar degree, suggesting no decrease in the efficacy of the agent over the 3-week treatment period. The apparent decrease in clinical response in patients treated with chlorpheniramine for 3 days versus 3 weeks was, in fact, related to a gradual decrease in compliance with therapy. This non-compliance was associated with the adverse effects of chlorpheniramine, including drowsiness, lightheadedness, and anticholinergic effects such as dry mouth and urinary hesitancy. Thus, the adverse effects of these first-generation antihistamines may interfere with their long-term value in treating allergic disease.

The current clinical role of first-generation antihistamines is controversial, because safer second-generation drugs are available. Some physicians administer a single dose of a first-generation H₁-antagonist at bedtime as a cost-saving measure, because the sedative effects will occur during sleep and H₁-blockage persists longer than sedation. No data exist regarding the efficacy or safety of combinations of morning dosing of second-generation antihistamines such as terfenadine with evening dosing of sedating antihistamines such as chlorpheniramine as a treatment for allergic rhinitis.

A study of the effects of antihistamines on children's learning demonstrated that the second-generation antihistamine loratadine caused significantly less learning impairment than the first-generation antihistamine diphenhydramine.^{21a} As the presence of allergic rhinitis, irrespective of therapy, induced a reduction in learning ability of children, further aggravation of impaired learning performance likely occurs with use of nightly administration of a sedating antihistamine, the effects of which on alertness may persist into the morning after the nighttime dosage.

The use of sedating antihistamines has also been associated with increased occupational injuries at

TABLE II. Risk factors for cardiovascular adverse effects of terfenadine and astemizole

Drug interactions involving hepatic cytochrome P450 metabolism
Imidazole antifungals, including ketoconazole and itraconazole
Macrolide antibiotics, including erythromycin and clarithromycin
Cimetidine
Natural flavonoids (grapefruit juice)
Overdose
Underlying cardiac abnormality
Prolonged QT interval
Ischemic heart disease
Congestive heart failure
Antiarrhythmic medications (quinidine)
Metabolic abnormalities
Hypokalemia (diuretic use)
Hypomagnesemia
Anorexia, liquid protein diet
Hepatic insufficiency, cirrhosis
Impaired metabolism in elderly persons

work.^{21b} In a study conducted in 1992 and 1993 by the Group Health Cooperative of Puget Sound, the single greatest increase in work-related injury occurred among users of sedating antihistamine, with the risk of injury being enhanced at an odds ratio of 1.5 (confidence interval 1.1 to 1.9) using conditional logistic regression to estimate the risk of traumatic injury, including open wounds, fractures, and burns after medication usage. Surprisingly, the risk of injury after first-generation antihistamine use was greater than that after use of sedative hypnotics or narcotics.^{21b}

Whereas some reports indicate adverse CNS effects appear to wane ≥ 8 hours after ingestion,²² other reports indicate that subjective drowsiness still occurs the morning after use.²³ Tolerance to the CNS side effects does not necessarily develop²⁴; impairment of CNS function occurs in the absence of obvious symptoms^{25, 26}; and there are data implicating these medications as a cause of fatal traffic accidents.^{26, 27}

Regimens utilizing morning dosing of second-generation antihistamines with evening dosing of first-generation antihistamines should not be advocated as a cost-saving measure until further studies determining the safety and efficacy of such regimens are conducted. The potential adverse consequences of daily use of a nightly first-generation antihistamine, including the possibility of fatal traffic accidents and work-related injury, mitigates against such AM/PM mixed antihistamine regimens. It is essential that protocols combining first- and second-generation antihistamines for cost savings do not adversely affect the quality of care or place the patient at unnecessary risk for potential adverse events from the nighttime first-generation antihistamine therapy.

Second-generation antihistamines

The second-generation drugs represent a significant therapeutic advance because of their more favorable risk-benefit ratio. Although they share some common features at H_1 -receptor sites, their actions are unlike those of classic antihistamines in the relative absence of cholinergic and serotonergic effects.

Because the second-generation H_1 -receptor antagonists have little or no affinity for muscarinic cholinergic receptors, they do not cause dry mouth or other anticholinergic effects such as gastrointestinal side effects. Most do not have antiserotonin activities and do not cause appetite stimulation or inappropriate body weight gain. However, this side effect has been reported after use of astemizole or ketotifen.^{28, 29}

These second-generation antihistamines vary considerably in their pharmacokinetic and pharmacodynamic profiles (Table I). Resistance over time has not been noted with these agents. The effects of these drugs on peripheral H_1 -receptor blockade in the skin^{9, 30, 31} and in allergic rhinitis³² do not decrease markedly with time in studies lasting 4 to 12 weeks.

The timing of administration can influence the efficacy of antihistamines. Terfenadine or clemastine given at 7 PM is more effective than when given at 7:00 AM in inhibiting the wheal response in the skin and in inhibiting erythema.³³ Given a choice, a single dose may be prescribed more appropriately for evening administration than for morning administration.

The quantity of allergen can also influence their efficacy. At peak pollen season, the efficacy of terfenadine is usually lost, and the efficacy of other antihistamines including astemizole may be markedly diminished. In contrast, in a study of olive pollen allergy in Greece, cetirizine still demonstrated significant efficacy in controlling symptoms at peak pollen season.³⁴

In addition to blocking the effects of histamine, there is some evidence that some of these newer drugs interfere with mediator release from allergic inflammatory cells, adding to their clinical benefit. Two of the symptoms of the allergic response, sneezing and rhinorrhea, are equally well controlled with first- and second-generation H_1 antagonists. In addition, another symptom of the allergic response, nasal congestion, may be controlled to some degree by the second-generation drug cetirizine.³⁵

PHARMACOKINETICS

Terfenadine and Fexofenadine

Terfenadine was the first second-generation antihistamine to be marketed and is a reference drug when other second-generation antihistamines are assessed. Terfenadine is metabolized extensively by the cytochrome P_{450} CYP3A4 hepatic mixed-function oxidase system by C-oxidation to an active acid metabolite (terfenadine carboxylate or terfenadine metabolite I) and by N-dealkylation to an inactive metabolite. On the first pass through the liver, 99% of terfenadine is metabolized. The active carboxylic acid metabolite, terfenadine me-

tabolite I, has a distribution phase of 2 to 4 hours and elimination phase of 17 hours and has some of the antihistaminic activity of terfenadine. The active metabolite called fexofenadine has recently been approved by the Food and Drug Administration as a potential therapeutic agent because it lacks the adverse cardiac complications of the parent compound.^{36a} Terfenadine rapidly gained popularity after its introduction; however, recent data demonstrating potential adverse drug interactions with potentially fatal arrhythmias have caused concern with respect to its widespread use. Fexofenadine has been demonstrated to have equal efficacy when dosed twice daily at 60, 120, or 240 mg as therapy for patients with modest to severe symptoms of fall seasonal rhinitis. No dose-response relationship with symptom reduction was noted, individual symptoms of allergic rhinitis including nasal congestion decreasing when compared to placebo. Additionally, no electrocardiogram abnormalities, including QT prolongation, were noted even at dosages of 480 mg/day of fexofenadine.^{36a}

Astemizole

Astemizole is unusual in that it has a very prolonged duration of action. Its therapeutic activity may take about 4 weeks to reach a steady state; therefore, it is not a good choice for intermittent treatment. In wheal-and-flare response tests, the wheal response can take as long as 8 weeks to recover to normal. Even at 8 weeks, the flare response may be recovered by only 30% to 40%. Similar long-lasting effects have been noted in the suppression of histamine-induced bronchospasm after 2 weeks of astemizole therapy. This drug also is significantly selective for peripheral versus central histamine receptors. Terfenadine, fexofenadine, loratadine, and cetirizine are more rapidly effective, with an onset of action within hours, whereas astemizole's onset of action occurs within 2 days and reaching peak efficacy in 4 days. Appetite stimulation induced by astemizole has been reported by some patients and may be similar to that induced by doxepin.³⁷ Astemizole has a drug interaction profile similar to that of terfenadine, but it poses the added concern of its prolonged half-life, which can lead to drug accumulation as a result of drug interactions or accidental overdose.

Astemizole has extensive first-pass metabolism by the liver; its major metabolite is desmethylastemizole. It is highly bound (about 97% bound) to plasma proteins.²⁹ Hepatic dysfunction increases astemizole levels, and increased levels pose a risk of cardiac arrhythmias. Furthermore, it is poorly dialyzable due to high protein binding should accidental overdose occur.

Loratadine

Loratadine, structurally related to azatadine, is a selective peripheral H_1 -receptor antagonist. It is equal in clinical efficacy to earlier antihistamines such as clemastine and to terfenadine. Loratadine was found to be 10 times less potent against central than peripheral H_1 -receptors.³⁸

For seasonal allergic rhinitis, a 10 mg dose is approved. This dose appears to be optimal for seasonal allergic

rhinitis, but higher doses may have greater bronchoprotective effects for histamine-induced bronchospasm.

Loratadine undergoes significant first-pass hepatic metabolism to a descarboxyethoxyloratadine. Cardiac side effects, such as QT prolongation and ventricular arrhythmias, have not been reported consequent to either drug overdosage or drug interaction such as with imidazole antifungal agents or macrolide antibiotics. The half life is 7 to 11 hours, making it appropriate for once-daily dosage, especially because the clinical half-life of blockage of the histamine-induced wheal response for loratadine is 24 hours. The serum half-life is prolonged in elderly persons, and drug levels may be increased when administered with macrolide antibiotics or imidazole antifungal agents.

Acrivastine

Acrivastine is a side-chain-reduced metabolite of the classic antihistamine triprolidine. Because its half-life is 1.4 to 2.1 hours, it requires more frequent dosing—four times daily—than other second-generation antihistamines. Distribution studies indicate that it penetrates the CNS poorly. A study of its effects indicated that acrivastine alone at a dose of 8 mg did not decrease CNS performance.³⁹ The metabolic fate of acrivastine is to excretion, largely unchanged, in the urine. Limited information about adverse effects with acrivastine has been published, but there are no published reports of ventricular arrhythmias, and studies using enhanced dosages of acrivastine have not demonstrated QT prolongation or other adverse cardiac consequences.²⁰

Cetirizine

Cetirizine is the carboxylic acid metabolite of hydroxyzine. Three important features characterize this antihistamine: a high specificity for the H₁-receptor, a low level of metabolism, and the existence of non-H₁-dependent activities on cells involved in the pathogenesis of allergy. The selectivity of cetirizine for H₁-receptors has been demonstrated. This drug has less binding to serotonin, dopamine, and α -adrenergic receptors than several other antihistamines including terfenadine and hydroxyzine.¹⁴

Cetirizine is unique among second-generation antihistamines in that it has primarily renal elimination; 70% of the drug appears unchanged in urine by 72 hours. The elimination half-life of cetirizine is short (7 hours in children and 10.6 hours in adults). Chronic renal failure can prolong the half-life to approximately 19 hours.

Although the liver does not play as significant a role in the elimination of cetirizine as in the elimination of astemizole, terfenadine, and loratadine, the pharmacokinetics of cetirizine are altered in patients with hepatic dysfunction.⁴⁰ Although therapeutic dose-ranging of cetirizine in relief of allergic rhinitis when 5, 10, and 20 mg/day are administered has been demonstrated, unlike the lack of dose-ranging efficacy seen with fexofenadine, only the 5 and 10 mg daily dose are FDA approved as therapy for rhinitis.³⁵

CARDIOVASCULAR SIDE EFFECTS

Concomitant administration of some H₁-receptor antagonists with medications known to inhibit biotransformation in the hepatic mixed-function oxygenase cytochrome P₄₅₀ CYP3A4 enzyme system can result in drug interactions. This enzyme system is a primary mechanism for the detoxification and removal of drugs from the body; some drugs must be activated by these enzymes before they show biologic activity. As a result of genetic variability, the number of P₄₅₀ isoenzymes varies, so specific drugs are metabolized differently. Liver damage or dysfunction and some drugs can inhibit the action of cytochrome P₄₅₀ enzymes; this inhibition may prolong the half-life of a drug, increase its duration of action, and cause adverse reactions. These enzymes can also be inhibited by naturally occurring flavonoids present in grapefruit juice.⁴¹

Cetirizine and fexofenadine are metabolized minimally by the liver. This is unique among the second-generation H₁-antagonists, and is a clinically significant advantage. Drug interactions involving potentiation or down-regulation of metabolic enzyme systems have not been reported or discovered in dose-response studies with cetirizine.⁴² Dose-response studies with cetirizine given as 20 and 60 mg doses (two and six times greater than recommended, respectively) did not produce prolongation of the QT_c interval.⁴² Dosage of up to 480 mg fexofenadine also has not affected the QT_c interval.^{36a}

Drugs that inhibit the P₄₅₀ enzymes and prolong the half-life of unchanged terfenadine, astemizole, and loratadine, preventing or slowing their activation are (1) ketoconazole, itraconazole, and possibly other imidazole antifungal agents; and (2) erythromycin, clarithromycin, troleandomycin, and possibly other macrolide antibiotics.

Among the second-generation antihistamines, only terfenadine and astemizole have been reported to induce QT prolongation. Because there is a link between terfenadine concentrations and the observed increase in QT_c interval, cardiotoxic concentrations of terfenadine can be seen with concomitant administration of ketoconazole,⁴³ erythromycin,⁴⁴ and clarithromycin. In both cases, a significant increase in the mean area under the curve of terfenadine carboxylate occurred. There is some suggestion that polymorphic ventricular tachycardia or torsades de pointes can occur also with large doses of some first-generation antihistamines such as diphenhydramine.³⁶

Arrhythmias can also occur with excess doses, hypokalemia (diuretic-induced) hypomagnesemia, and congenital prolonged QT syndromes. Patients taking medications that prolong the QT interval (e.g., quinidine) are also at increased risk.

Variables within the patient may be important in the development of adverse cardiovascular effects from second-generation H₁-antagonists (Table II). An intrinsically increased risk occurs in patients with a prolonged QT interval (congenital or secondary to coronary heart disease or hyperthyroidism) and those with alcoholic

liver disease (who are at risk of QT prolongation and increased risk of sudden cardiac death and who have a diminished ability to metabolize H_1 -receptor antagonists).⁴⁵ Situations requiring caution are patients taking more than one antihistamine, patients with hypertension requiring a diuretic, patients with hypokalemia or hypomagnesemia, and those taking drugs such as antiarrhythmic agents. Persons taking liquid protein diets or persons with anorexia may have metabolic and electrolyte disturbances that increase the risk for ventricular arrhythmia.³⁶

Clearly, increased caution should be exercised in prescribing a drug with a life-threatening complication for a non-life-threatening condition. However, considering the millions of patients who are taking second-generation antihistamines, potentially life-threatening adverse effects are quite rare. In a study of 1.1 million exposures to terfenadine among 596,000 recipients of Medicaid, there were 1.6 excess life-threatening ventricular arrhythmia events per 10,000 terfenadine exposures.⁴⁶ Further, a pharmacoepidemiologic study of terfenadine found that QT_c prolongation >440 msec was linked with coadministration of erythromycin or coexisting cardiovascular disease.⁴⁷ Although the adverse event rate was similar for terfenadine and other H_1 -antihistamines, this study reported 1 sudden death, 27 syncopal episodes, and 33 episodes of ventricular arrhythmia with terfenadine administration.

Of the 250 cases of cardiovascular complications reported by 1993 after terfenadine ingestion, most were due to large doses of the drug, drug interactions with ketoconazole or itraconazole, cirrhosis, or multiple risk factors.²⁰ However, coadministration of terfenadine with either ketoconazole or macrolide antibiotics may still occur despite the 1990 "Dear Doctor" letter warning physicians of these interactions.⁴⁸ A recent retrospective review of computerized pharmacy claims found the overlapping use of terfenadine with contraindicated drugs such as erythromycin to be 2.3 per 100 persons; this rate had declined by 57% from 1990 to 1994.⁴⁹

Cases of torsades de pointes after astemizole use have also been reported, usually linked to large doses or overdose, preexisting cardiac problems, hepatic dysfunction (including cirrhosis), or metabolic dysfunction.²⁰ Astemizole's long half-life (104 hours) and its slow clearance may increase the risk for potential adverse effects.³⁶ Problems with torsades de pointes have not been reported after use of loratadine, acrivastine, or cetirizine.²⁰

Dose-response studies of terfenadine indicate high doses (180 to 300 mg) were associated with significant prolongation of the QT_c interval, but these were not seen using 60 mg terfenadine.⁵⁰ A study of 241 patients found that in 75% who took terfenadine and erythromycin concomitantly, torsades de pointes or other cardiac abnormalities did not develop.⁵¹ This finding may be explained by individual differences in electrophysiologic features of myocardial cells or in the cytochrome P_{450} isoenzymes that metabolize terfenadine.⁴⁸

As a clinician treating these patients, it is impossible

to know who will and who will not have cardiotoxic complications. Clinical symptoms of antihistamine-associated arrhythmias induced by QT prolongation include dizziness, lightheadedness, syncope or collapse, irregular heartbeat or palpitations, and possible sudden death. An electrocardiogram is required to diagnose these arrhythmias, including torsades de pointes.³⁶

A diagnostic and predictive marker for this condition is a prolonged QT interval on the electrocardiogram, which precedes the development of torsades de pointes in most patients.⁵²

Like some of the other second-generation antihistamines, loratadine's metabolism is inhibited by erythromycin and by antifungal drugs. Significantly increased plasma concentrations of loratadine occur when this drug is administered concurrently with ketoconazole, erythromycin, or cimetidine. However, no significant effects on QT_c intervals have been associated with an increase in the area under the curve of this drug. The reason may be that loratadine, unlike terfenadine, does not block the delayed rectifier potassium channel in the cardiac conduction system even at much greater concentrations than encountered clinically.⁵³ It may be that loratadine has unique effects on histamine receptors in the heart.

Loratadine, acrivastine, cetirizine, or fexofenadine may be safe alternatives to continued therapy with terfenadine or astemizole in patients at risk of torsades de pointes. Cetirizine, which is largely excreted essentially unchanged by the kidneys, may be safer for patients with liver dysfunction than other antihistamines, which are more dependent on hepatic metabolism for their elimination.³⁶

ANTIALLERGIC ACTIVITIES

Although they are called "antihistamines," some of these drugs may have actions beyond their ability to compete with histamine for H_1 -receptor sites. Azatadine, a first-generation antihistamine, was the first antihistamine demonstrated to possess antiallergic properties, including down-regulation of leukotriene C_4 production consequent to the immediate allergic response.⁵⁴ In vitro data show that terfenadine may inhibit the release of leukotrienes from isolated basophils and eosinophils stimulated with anti-IgE or ionophore, suppress histamine release from purified basophils, and suppress skin-test reactivity to PAF. Loratadine has also been reported to have antiallergic effects, including suppression of histamine release from isolated basophils and inhibition of ICAM-1 expression on endothelial cells, as well as inhibition of release of leukotrienes and PGD_2 .⁵⁵ The clinical relevance of these effects is uncertain because high dosages are necessary to produce some effects. Using usual clinical doses of H_1 antagonists, the concentrations that achieve these in vitro effects are as much as 1000 times higher than can be achieved in vivo.¹ Because these drugs are highly protein bound, it is uncertain whether sufficient drug concentrations can be achieved within basophils to modulate cell activation. In addition, studies of isolated, purified, inflammatory cell responses to these antihistamines may not mirror the in vivo responses achieved.

Cetirizine has antiallergic effects that have been observed in clinically relevant doses. A unique property of cetirizine may be its ability to inhibit the infiltration of eosinophils, key cells in the pathogenesis of the allergic LPR.⁵⁶ In experimental cutaneous models, 12 to 48 hours after the injection of an allergen into a patient sensitized to the allergen eosinophils infiltrate the injection site; cetirizine inhibits part of this eosinophil infiltration.⁵⁷ In skin chamber experiments, cetirizine exhibited independent antiinflammatory, antiallergic properties, such as inhibition of the last-phase recruitment of eosinophils, neutrophils, and basophils⁵⁸ and inhibition of the late-phase appearance of histamine at allergen challenge sites.⁵⁶ These experiments, conducted at clinically relevant doses, suggest that cetirizine, beyond its role as a histamine antagonist, may suppress the LPR. The mechanism of action of cetirizine may be in controlling endothelial eosinophil adhesion by modulation of ICAM-1 expression. A parallel reduction in ICAM-1 expression and reduction in allergy symptom scores was noted in a model using conjunctival allergen challenge in patients pretreated with cetirizine. The allergen-mediated cellular influx of eosinophils and lymphocytes was also suppressed in the cetirizine-treated cohort.⁵⁹

Cetirizine blocks the response in skin to PAF, an important chemotactic mediator in late-phase inflammation and diminishes the production of wheal-and-flare response by PAF.^{60,61} Patients with asthma have platelets that can release (on challenge with appropriate stimuli) toxic mediators capable of killing a biologic target (larvae of *Schistosoma mansoni*). Of interest, cetirizine significantly inhibited this in vitro killing phenomenon.⁶² Neither loratadine or dexchlorpheniramine had similar effects.

Cetirizine may also have an antiinflammatory effect in decreasing TAME-esterases (released concomitantly with mast-cell tryptase but not necessarily derived from mast cells), which are increased during immediate allergic responses.⁶³ TAME-esterase activity in nasal secretion parallels vascular permeability; increased levels of TAME-esterase are also found in the LPR.

Leukotriene levels are reduced by azelastine and cetirizine. These drugs do not inhibit mast-cell activation, so cells other than mast cells, most likely eosinophils and perhaps basophils and macrophages, contribute to the production of these leukotrienes. It is known that histamine itself does not affect LTC₄ production, so these antihistamines must block antigen-induced LTC₄ production, thereby dampening the acute allergic response.⁶⁴ This effect may be related to the decreased traffic of inflammatory cells into the site of the allergic response, including eosinophils, basophils, and macrophages, all of which are capable of leukotriene production.

ANTIASTHMATIC EFFECTS

There is a long-held belief that antihistamines may be harmful in asthmatic patients. Some of this skepticism

comes from the mucosal-drying and anticholinergic effects of older preparations. However, because histamine is known to be a bronchoconstricting substance in asthma and to increase leakage of postcapillary venules leading to edema,⁶⁵ it is logical that antihistamines could reverse some of the harmful effects of histamine in patients with an allergic component to their asthma. There is evidence that even some of the classic drugs may be beneficial in asthma. Intravenous chlorpheniramine achieved a 10% increase in FEV₁ and a 20% to 30% increase in the midmaximum expiratory flow rate, which lasted as long as 3 hours.⁶⁶ Nebulized chlorpheniramine achieved bronchodilation and increased peak flow rate but induced coughing initially.⁶⁷

Indication of the potential adverse effects of antihistamines came from a study that demonstrated the induction of asthma in some children who used antihistamines. Schuller⁶⁸ identified 10 children who had adverse responses of antihistamines from a population of 500 asthmatic children in her practice. These children had baseline small-airway function that was essentially normal, but a modest increase in bronchoconstriction developed after brompheniramine administration with or without decongestant use. In these children there was an approximately 30% decline in FEV₁ at 60 minutes that gradually improved at 120 minutes. Other asthmatic children had a modest rise in air flow and FEV₁. Schuller's results have not been confirmed by other investigators.^{66,69,70} The American Academy of Allergy, Asthma, and Immunology⁷¹ has issued a position paper stating that antihistamines are not contraindicated in asthma unless previous adverse reactions have been observed.

Studies with newer agents that do not have prominent anticholinergic effects at higher doses than now clinically recommended have demonstrated an increase in FEV₁, including studies lasting >2 hours with terfenadine, which was effective in a dose-dependent manner. Clinical studies support the view that newer antihistamines may be helpful in asthma including favorable results with cetirizine,^{72,73} azelastine⁷⁴ and to a lesser extent, terfenadine and astemizole.⁷⁵ These agents do not affect nonspecific airway reactivity and fail to protect against methacholine-induced bronchospasm. However, terfenadine has been shown to block exercise-induced bronchospasm in a dose-dependent manner and to inhibit asthma symptoms during grass pollen season when administered at doses significantly exceeding those recommended.⁷⁶ Astemizole, when clinically administered, also reduces allergen-induced immediate bronchospasm from 40% to 80% within 2 to 15 minutes after allergen challenge (probably inhibiting the histamine-mediated component of bronchospasm). It also diminishes exercise-induced bronchospasm.⁷⁷ Its prolonged duration of action in the skin is paralleled in the lung. Loratadine also blocks histamine-induced bronchospasm as well as exercise-induced bronchospasm.

The clinical relevance of blocking histamine-induced bronchospasm may be noted in patients who

have allergen-mediated bronchospasm. Astemizole reduces bronchoreactivity to dust-mite allergen at clinically relevant doses (10 mg/day)⁷⁸; however, the peak effect may take as long as 4 weeks to be noted. Cetirizine also protects against dust-mite-induced bronchospasm in allergic patients. Higher quantities of dust mite were required to induce bronchospasm in cetirizine-treated allergic persons with asthma.⁷⁹ Experimentally, high dosages of cetirizine diminishes eosinophil migration detected by bronchoalveolar lavage fluid after allergen challenge.⁸⁰

Cetirizine induces bronchodilation up to 120 minutes after oral administration. In patients given relatively high doses of cetirizine, β -agonist and corticosteroid requirements decreased and pulmonary symptom scores decreased in patients with pollen-induced asthma treated during pollen season.⁷³ It may be that cetirizine affects bronchospasm to varying degrees, depending on the degree of histamine-induced bronchospasm in an individual patient. It is reasonable to presume that several factors contribute to bronchial hyperresponsiveness and that these factors vary within individual persons with asthma at different times and vary among persons. A recent study by Grant et al.⁸¹ of patients with both asthma and rhinitis induced by ragweed pollen demonstrated that a 10 mg dose of cetirizine inhibited both rhinitis and asthma symptoms. No adverse effects were noted related to asthma in the cetirizine-treated patients, providing evidence of the safety of cetirizine when administered to patients with concomitant allergic rhinitis and asthma. The effect of cetirizine is additive to the effect of β_2 -agonists such as albuterol and is also dose dependent.⁸²

Because the importance of airway inflammation is now seen as prominent in asthma, cetirizine's effects on inflammatory cells and their bioactive mediators may give this drug an added advantage in asthma. Inflammatory cells of all types were reported to be significantly reduced in alveolar washings in cetirizine-treated patients with asthma compared with placebo-treated patients.⁵⁸

Although more than half of asthma patients have a late-phase airway obstruction occurring hours after allergen exposure, the effects of histamine in this LPR have not been fully elucidated. Further studies are warranted to define the antiasthmatic effects of antihistamines. The immediate airway response may be induced more by airway smooth-muscle contraction, whereas the airway LPR is more inflammatory having more prominent edema and hypersecretion in peripheral airways. The late-phase effects of H_1 -receptor antagonism, particularly with antihistamines, which have antiinflammatory actions, require further study. There may be a subset of patients who are particularly responsive to H_1 -receptor antagonists in asthma.

Antihistamines in practice

The selection of an ideal antihistamine in patients with allergic rhinitis should be based on these ideal

characteristics: no cardiotoxic or anticholinergic effects; rapid onset of action; once-daily administration; short half-life; lack of accumulation; lack of overly sustained effect in the skin allowing skin testing; predictably high efficacy; minimal drug interactions; and the fewest adverse effects due to the inhibition of metabolism or elimination.

There is added rationale for using an antihistamine that has antiinflammatory properties potentially adding to its therapeutic efficacy in patients with a prominent LPR or chronic inflammation. Typically, patients with chronic allergic disease or patients who have been exposed to high allergy concentrations in peak allergy season would benefit most from such additional antiasthmatic effects of antihistamines.

The results of recent studies indicate that we do not completely appreciate the full therapeutic potential of H_1 -receptor antagonists. The antiinflammatory and antiasthmatic actions of some of these agents will be more fully elucidated in the coming years. In the future, the use of antihistamines in medicine will take advantage of advances in our understanding of how these agents work beyond their effects in controlling the effects of histamine that occur consequent to interaction with H_1 -receptors.

REFERENCES

1. Simons EF, Simons KJ. The pharmacology and use of H_1 -receptor-antagonist drugs. *N Engl J Med* 1994;330:1663-9.
2. Turkeltaub PC, Gergen PJ. Prevalence of upper and lower respiratory conditions in the US population by social and environmental factors: data from the second National Health and Nutrition Examination Survey, 1976 to 1980: NHANES II. *Ann Allergy* 1991;67:147-54.
3. Meltzer EO. An overview of current pharmacotherapy in perennial rhinitis. *J Allergy Clin Immunol* 1995;95:1097-110.
4. Masheter HC. Terfenadine: the first second-generation antihistamine. *Clin Rev Allergy* 1993;11:5-34.
5. Wasserman SI. Histamine and the preclinical pharmacology of cetirizine. *Ann Allergy* 1987;59:1-3.
6. Arrang JM. Pharmacological properties of histamine receptor subtypes. *Cell Mol Biol* 1994;40:273-9.
7. Holgate ST, Abraham WM, Barnes PS, Lee TH. The role of inflammatory processes in airway hyperresponsiveness. ST Holgate, editor. Oxford: Blackwell, 1989:179-221.
8. Prenkowsky MM, Adkinson NF Jr, Plaut M, Norman PS, Lichtenstein LM. Prostaglandin D₂ and histamine during the immediate and late-phase components of allergic cutaneous response. *J Allergy Clin Immunol* 1988;82:95-100.
9. Watson WTA, Simons KJ, Chen XY, Simons FER. Cetirizine: a pharmacokinetic and pharmacodynamic evaluation in children with seasonal allergic rhinitis. *J Allergy Clin Immunol* 1989;84:457-64.
10. Howarth PH, Emanuel MB, Holgate ST. Astemizole, a potent histamine H_1 -receptor antagonist: effect in allergic rhinoconjunctivitis, on antigen and histamine induced skin wheal responses and relationship to serum levels. *Br J Clin Pharmacol* 1984;18:1-8.
11. Simons FER, Murray HE, Yi Z, Simons KJ. Cetirizine and

- hydroxyzine concentrations in human skin [abstract]. *J Allergy Clin Immunol* 1994;93:222.
12. Simons FER, Simons KJ. Pharmacokinetic optimization of histamine H₁-receptor antagonist therapy. *Clin Pharmacokinetics* 1991;21:372-93.
13. De Vos C, Malefix M-R, Baltes E, Golbert J. Inhibition of histamine and allergen skin wheal by cetirizine in four animal species. *Ann Allergy* 1987;59:278-82.
14. Naclerio RM, Porud D, Kagey-Sobotka A, Freidhoff L, Norman PS, Lichtenstein LM. The effect of cetirizine on early allergic response. *Laryngoscope* 1989;99:596-9.
15. Canonica GW, Pronzato C, Fiorino N, Ciprandi G, Bagnasco M. Adhesional molecules: a review of their clinical roles in allergic inflammation. *ACI News* 1993;5:80-4.
16. Simons FR, McMillan JL, Simons KJ. A double-blind, single-dose crossover comparison of cetirizine, terfenadine, loratadine, astemizole, and chlorpheniramine versus placebo, suppression effects on histamine-induced wheals and flares during 24 hours in normal subjects. *J Allergy Clin Immunol* 1990;86:540-7.
17. Meltzer EO. Antihistamine and decongestant-induced performance decrements. *J Occupational Med* 1990;32:327.
18. Wyngaarden JB, Seavers MH. The toxic effects of antihistaminic drugs. *JAMA* 1951;145:277-82.
19. Meltzer EO. Comparative safety of H₁-receptor antihistamines. *Ann Allergy* 1991;67:625-33.
20. Simons FER. H₁-receptor antagonists: comparative tolerability and safety. *Drug Safety* 1994;10:350-80.
21. Bantz EW, Dolen WK, Chadwick EW, Nelson HS. Chronic chlorpheniramine therapy: subsensitivity, drug metabolism and compliance. *Ann Allergy* 1987;59:341-6.
- 21a. Vuorman EPPM, van Veggel LMA, Uiterwijk MMC, Leutner Detlev, O'Hanlon JF. Seasonal allergic rhinitis and antihistamine effects on children's learning. *Ann Allergy* 1993;71:121-6.
- 21b. Gilmore TM, Alexander BH, Mueller BA, Revara FP. Occupational injuries and medication use. *Am J Industrial Med* 1996;30:234-9.
22. Alford C, Rombaut N, Jones J, Foley S, Idzikowski C, et al. Acute effects of hydroxyzine on nocturnal sleep and sleep tendency the following day: a C-EEG study. *Human Psychopharmacol* 1992;7:25-35.
23. Goetz DW, Jacobson JM, Apaliski SJ, Repperger DW, Martin ME. Objective antihistamine side effects are mitigated by evening dosing of hydroxyzine. *Ann Allergy* 1991;67:448-54.
24. Goetz DW, Jacobson JM, Mumane JE, et al. Prolongation of simple and choice reaction time in a double-blind comparison of twice-daily hydroxyzine versus terfenadine. *J Allergy Clin Immunol* 1989;84:316-22.
25. Seidel WF, Cohen S, Bliwise NG, Dement WC. Direct measurement of daytime sleepiness after administration of cetirizine and hydroxyzine with a standardized EEG assessment. *J Allergy Clin Immunol* 1990;86:1029-33.
26. Cimbura G, Lucas DM, Bennett RC, Warren RA, Simpson HM. Incidence and toxicological aspects of drugs detected in 484 fatally injured drivers and pedestrians in Ontario. *Forensic Sci* 1982;27:855-67.
27. Warren R, Simpson H, Hilchie J, Cimbura G, Lucas D, et al. Drugs detected in fatally injured drivers in the province of Ontario. In: Goldburg L, editor. *Alcohol, drugs and traffic Safety*, vol. 1. Stockholm: Almqvist & Wiksell, 1981:203-17.
28. Grant SM, Goa KL, Fitton A, Sorking EM. Ketotifen: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in asthma and allergic disorders. *Drugs* 1990;40:412-48.
29. Janssens MM-L. Astemizole: a non-sedating antihistamine with fast and sustained activity. *Clin Rev Allergy* 1993;11:35-63.
30. Simons FER, Watson WTA, Simons KJ. Lack of subsensitivity to terfenadine during long-term terfenadine treatment. *J Allergy Clin Immunol* 1988;82:1068-75.
31. Bousquet J, Chanal I, Skass-Brociek W, Lemonier C, Michel FB. Lack of subsensitivity to loratadine during long-term dosing during 12 weeks. *J Allergy Clin Immunol* 1990;86:248-53.
32. Juniper EF, White J, Dolovich J. Efficacy of continuous treatment with astemizole and terfenadine in ragweed pollen-induced rhinoconjunctivitis. *J Allergy Clin Immunol* 1988;82:670-5.
33. Sorkin BM, Heel RC. Terfenadine: a review of its pharmacodynamic properties and therapeutic efficacy. *Drugs* 1985;29:34.
34. Panayotopoulos SM, Panayotopoulou ES. Efficacy of cetirizine in the treatment of seasonal allergic rhinoconjunctivitis. *Ann Allergy* 1990;65:146-8.
35. DuBuske LM. Dose-ranging comparative evaluation of cetirizine in patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 1995;74:345-53.
36. Smith SJ. Cardiovascular toxicity of antihistamines. *Otolaryngol Head Neck Surg* 1994;111:348-54.
- 36a. Bernstein DI, Schoenwetter W, Nathan R, et al. Fexofenadine: a new nonsedating antihistamine is effective in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol* 1996;97:435.
37. Busse W. Role of antihistamines in allergic disease. *Ann Allergy* 1994;72:371-5.
38. Mauser PJ, Kreutner W, Egan RW, Chapman RW. Selective inhibition of peripheral histamine responses by loratadine and terfenadine. *Eur J Pharmacol* 1990;182:125-9.
39. Cohen AF, Hamilton M, Phillipson R, Peck AW. The acute effects of acrivastine (BW825C), a new antihistamine compared with triprolidone on measures of CNS performance and subjective effects. *Clin Pharmacol Ther* 1985;38:381-6.
40. Spencer CM, Faulds D, Peters DH. Cetirizine: a reappraisal of its pharmacological properties and therapeutic use in selected allergic disorders. *Drugs* 1993;46:1055-80.
41. Guengerich FP, Kim DH. In vitro inhibition of dihydropyridine oxidations and aflatoxin B₁ activation in human liver microsomes by naringenin and other flavonoids. *Carcinogen* 1992;11:2275-9.
42. Sale ME, Woosley RL, Barby JT, Yeh J, Chung M. Lack of electrocardiographic effects of cetirizine in healthy humans. *J Allergy Clin Immunol* 1993;91:258.
43. Honig PK, Wortham DC, Zamani K, Conner DP, Mullin JC, Cantilena LR. Terfenadine-ketoconazole interaction. *JAMA* 1993;269:1513-8.
44. Honig PK, Woosley RL, Zamani K, Conner DP, Cantilena LR Jr. Changes in the pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine with concomitant administration of erythromycin. *Clin Pharmacol Ther* 1992;52:231-8.
45. Day CP, James OFW, Butler TJ, Campbell RWF. QT prolongation and sudden cardiac death in patients with alcoholic liver disease. *Lancet* 1993;341:1423-8.
46. Pratt CM, Hertz RP, Ellis BE, Shaw M, Crowell SP, et al. What is the risk of developing life-threatening ventricular

- arrhythmia on terfenadine? interpretation and limitations of an observational cohort study. *Am J Cardiol*, 1994. In press.
47. Hanrahan JP, Choo PW, Carlson W, Greineder D, Faich GA, et al. Antihistamine-associated sudden death, ventricular arrhythmias, syncope and QT-prolongation: a comparison of terfenadine and other antihistamines. *Postmarketing Surveillance* 1992;6:23-4.
48. Honig PK, Wortham DC, Zamani K, Mullin JC, Conner DP, et al. The effect of fluconazole on the steady-state pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine in humans. *Clin Pharmacol Ther* 1993;53:630-6.
49. Thompson D, Oster G. Use of terfenadine and contraindicated drugs. *JAMA* 1996;275:1339-41.
50. Sanders RL, Dockhom RJ, Alderman JL, McSorley PA, Wenger TL, et al. Cardiac effects of acrivastine compared to terfenadine. *J Allergy Clin Immunol* 1992;89:183.
51. Piepho RW. Current status of second-generation antihistamines. *Intern Med Alert* 1993;15/16:126-7.
52. Ben-David J, Zipes DP. Torsades de pointes and proarrhythmia. *Lancet* 1993;341:1578-82.
53. Good AP, Rockwood R, Schad P. Loratadine and ventricular tachycardia. *Am J Cardiol* 1994;74:207-9.
54. Togias AG, Naclerio RM, Warner J, et al. Demonstration of inhibition of mediator release from human mast cells by azatadine base: in vivo and in vitro evaluation. *JAMA* 1986;255:225-9.
55. Bousquet J, Lebel B, Chaneil I, Morel A, Michel FB. Antiallergic activity of H₁-receptor antagonists assessed by nasal challenge. *J Allergy Clin Immunol* 1988;82:881-7.
56. Michel L, DeVos C, Dubertret L. Cetirizine effects on the cutaneous allergic reaction in humans. *Ann Allergy* 1990;65:512-6.
57. Charlesworth EN, Kagey-Sobotka A, Nonnan PS, et al. Effect of cetirizine on mast cell mediator release and cellular traffic during the cutaneous late-phase reaction. *J Allergy Clin Immunol* 1989;83:905-12.
58. Redier H, Chanez P, DeVos C, et al. Inhibitory effect of cetirizine on the bronchial eosinophil recruitment induced by allergen inhalation challenge in allergic patients with asthma. *J Allergy Clin Immunol* 1992;90:215-24.
59. Ciprandi G, Buscaglia S, Pesce G, et al. Ceterizine reduces inflammatory cell recruitment and ICAM-1 (or CD54) expression on conjunctival epithelium in both early- and late-phase reactions after allergen-specific challenge. *J Allergy Clin Immunol* 1995;95:612-21.
60. Fadel R, David B, Herpein-Richard N, et al. Effects of cetirizine on human eosinophil and neutrophil activation in vitro. *Int Arch Allergy Appl Immunol* 1991;95:158-62.
61. Walsh GM, Moqbel R, Harmell A, et al. Effects of cetirizine on human eosinophil and neutrophil activation in vitro. *Intern Arch Allergy Appl Immunol* 1991;95:158-62.
62. Coyle A J, Lefort J, Vargaftig BB. The effect of cetirizine on antigen-dependent leukopenia in the guinea-pig. *Br J Pharmacol* 1991;103:1520-4.
63. Togias AG, Proud D, Kagey-Sobotka A, Freidhoff L, Lichtenstein LM, Naclerio RM. In vivo and in vitro effects of antihistamines on mast cell mediator release: a potentially important property in the treatment of allergic disease. *Ann Allergy* 1989;63:465-89.
64. Naclerio RM. The effect of antihistamines on the immediate allergic response. *Otolaryngol Head Neck Surg* 1993;108:723-30.
65. Tucker A, Weir EK, Reeves JT, Grover RF. Histamine H₁- and H₂-receptors in pulmonary and systemic vasculature of the dog. *Am J Physiol* 1975;229:1008-13.
66. Popa VT. Bronchodilating activity of an H₁ blocker, chlorpheniramine. *J Allergy Clin Immunol* 1977;59:54-63.
67. Groggins RC, Milner AD, Stokes GM. The bronchodilator effects of chlorpheniramine in childhood asthma. *Br J Dis Chest* 1979;73:297-301.
68. Schuller DE. Adverse effects of brompheniramine on pulmonary function in a subset of asthmatic children. *J Allergy Clin Immunol* 1983;72:175-9.
69. Lewiston NJ, Johnson S, Sloan E. Effect of antihistamines on pulmonary function of children with asthma. *J Pediatr* 1982;101:458-60.
70. Karlin JM. The use of antihistamines in asthma. *Ann Allergy* 1972;30:342-7.
71. American Academy of Allergy and Immunology. The use of antihistamines in patients with asthma. *J Allergy Clin Immunol* 1988;82:481-2.
72. Bousquet J, Emonot A, Germouty J, et al. Double-blind multicenter study of cetirizine in grass-pollen-induced asthma. *Ann Allergy* 1990;65:504-7.
73. Buttmann G, Pedrali P, Arendt C, Rihoux JP. Protective effect of cetirizine in patients suffering from pollen asthma. *Ann Allergy* 1990;64:224-8.
74. Storms W, Middleton E, Dvorin D, Kemp J, Spector SL, Newton J, et al. [abstract]. *J Allergy Clin Immunol* 1989;75:167.
75. Rafferty P, Holgate ST. Terfenadine (Seldane) is a potent and selective histamine H₁-receptor antagonist in asthmatic airways. *Am Rev Respir Dis* 1987;135:181-4.
76. Finnerty JP, Holgate ST. *Eur Respir J* 1989;140:593-7.
77. Clee MD, Ingram CG, Reid PC, Robertson AS. The effect of astemizole on exercise-induced asthma. *Br J Dis Chest* 1984;78:180-3.
78. Cistero A, Abadias M, Lieonaart R. Effect of astemizole on allergic asthma. *Ann Allergy* 1992;69:123-7.
79. Kopferschmitt-Kubler MC, Couchot A, Pauli G. Evaluation of the effect of oral cetirizine on antigen-induced immediate asthmatic responses. *Ann Allergy* 1990;65:501-3.
80. Redier H, Chanez P, DeVos C, Rifai N, Clauzel AM, et al. Inhibition of effect of cetirizine on the bronchial eosinophil recruitment induced by allergen inhalation challenge in allergic patients with asthma. *J Allergy Clin Immunol* 1992;90:215-24.
81. Grant JA, Nicodemus CF, Findlay SR, et al. Ceterizine in patients with seasonal rhinitis and concomitant asthma: prospective, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 1995;95:923-32.
82. Spector SL, Nicodemus CF, Corren J, Shanher HM, Rachelfsky GS, et al. Comparison of the bronchodilatory effects of cetirizine, albuterol, and both together versus placebo in patients with mild to moderate asthma. *J Allergy Clin Immunol* 1995;96:174-81.