LILY C. PIEN, MD
Department of Allergy and Immunology,
Cleveland Clinic

Appropriate use of second-generation antihistamines

ABSTRACT

Antihistamines, one of the most frequently used groups of medications in the United States, are primarily used in treating allergic rhinitis and urticaria and also anaphylactic reactions, pruritus, and symptoms of anxiety. Second-generation antihistamines are safe and effective for treating allergic conditions. Control of nasal congestion may require additional medication. Further studies will determine if second-generation antihistamines can be used for other medical conditions.

KEY POINTS

Compared with first-generation antihistamines, second-generation antihistamines are less likely to cross the blood-brain barrier and therefore produce less sedation.

Although the first two second-generation antihistamines (terfenadine and astemizole) were withdrawn because of drug interactions that increased the plasma levels of these agents and caused arrhythmias, newer agents appear to be free of significant interactions.

In allergic rhinitis, antihistamines are most effective if taken before allergen exposure. In the late phase (ie, several hours after exposure), inhaled corticosteroids may be more effective.

SECOND-GENERATION ANTIHISTAMINES have largely replaced first-generation antihistamines, for several reasons. Unlike the older agents, they have no appreciable effect on the central nervous system and therefore produce little or no sedation or anticholinergic effects. They are also longer-acting, and some of them have anti-inflammatory and antiasthmatic effects. In addition, the manufacturers are marketing them heavily to physicians and the general public, and patients are therefore asking for them by name.

We ought to keep several things in mind when prescribing these drugs. In some situations sedation is desirable, and first-generation antihistamines are often prescribed specifically for this purpose. In addition, in prescribing any drug we need to consider whether the drug is actually indicated: for example, antihistamines are generally not effective against the late-phase reaction of allergic rhinitis, and no second-generation antihistamine is officially indicated in treating the common cold.

This article reviews the five available second-generation antihistamines: acrivastine (Semprex-D), azelastine (Astelin), cetirizine (Zyrtec), fexofenadine (Allegra), and loratadine (Claritin).

HISTAMINE AND THE ALLERGIC REACTION

A person starts to become sensitized to an allergen when a T lymphocyte encounters the allergen and induces a B lymphocyte to produce a specific IgE antibody to it. The secreted IgE then attaches to mast cells via high-affinity receptors.

Thereafter, whenever the allergen is reintroduced, it binds to these receptor-bound IgE

How antihistamines prevent early-phase symptoms in allergic rhinitis

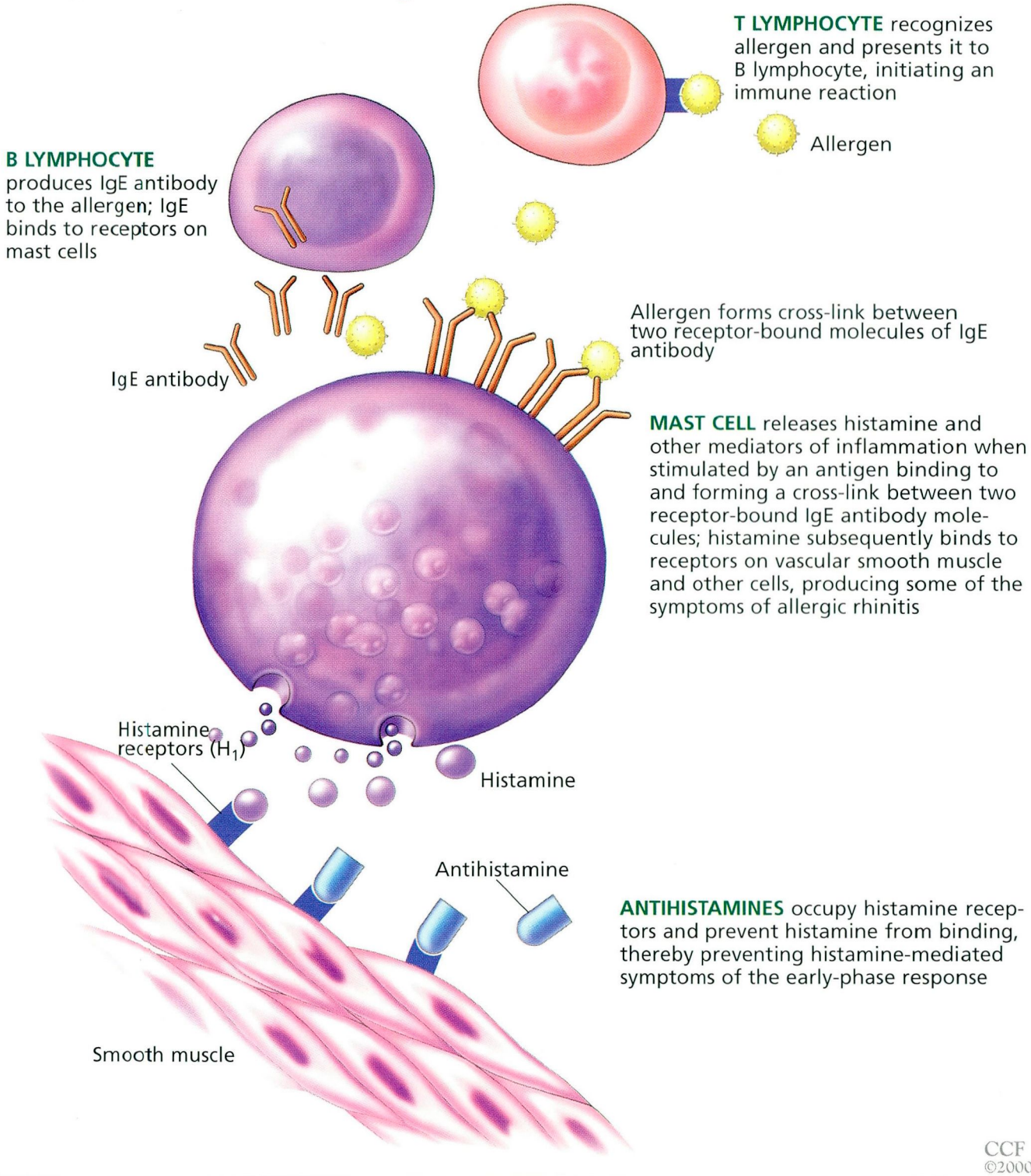


FIGURE 1

TABLE 1

Histamine receptors: Distribution, actions, and effects

H_1 receptors

Distribution
- Blood vessels
- Smooth muscle cells of the respiratory and gastrointestinal tracts
- Peripheral and central nervous system
- Heart

Actions
- Contraction of smooth muscle cells in the airway and gastrointestinal tract
- Dilatation and increased permeability of blood vessels
- Increased bronchial mucosal goblet cell secretion
- Prolonged AV node conduction time
- Increased cyclic GMP and prostaglandin generation
- Stimulation of vagal afferent nerves in the airway and cough receptors

Effects
- Mediate the symptoms of allergic rhinitis

H_2 receptors

Distribution
- Parietal cells of gastric mucosa
- Airway
- Heart
- Uterus
- Central nervous system

Actions
- Increased gastric acid secretion
- Esophageal relaxation
- Increased production of airway mucus
- Bronchial smooth muscle relaxation
- Positive chronotropic action of the atrium
- Inotropic action of the ventricle

Effects
- Symptoms of flushing, headache, hypotension, and tachycardia are mediated by activation of both H_1 and H_2 receptors

H_3 receptors

Distribution
- Central nervous system
- Airways
- Gastrointestinal tract
- Lymphoid tissues

Actions
- Control histamine synthesis and release
- Regulate serotonin, dopamine, noradrenaline, and acetylcholine

Effects
- Function still under investigation, but appears to be inhibitory

molecules and forms cross-linkages with them, activating the mast cell (FIGURE 1).

The resulting allergic response has two phases: early and late.

The early phase occurs within minutes of this subsequent allergen exposure, as the mast cells release already-formed inflammatory molecules (primarily histamine, but also tryptase, chymotryptase, and carboxypeptidases) from their granules. Production of other mediators of inflammation is also stimulated; these include leukotrienes such as LTB4 and LTC4, prostaglandin D2, platelet-activating factor, and various cytokines.

The histamine released subsequently binds to three types of receptors, designated H_1, H_2, and H_3, which are located in various tissues and have various effects (TABLE 1). The familiar symptoms of sneezing, pruritus of the nose, eyes, and ears, and clear watery rhinorrhea are mainly due to histamine binding to the H_1 receptor.

Antihistamines produce their desired effects by blocking the H_1 receptor, and for this reason they are sometimes called H_1 receptor antagonists. They are most effective if taken before allergen exposure, so that they can occupy the receptor site before histamine is released.

The late-phase reaction begins 4 to 6 hours later, as eosinophils, neutrophils, basophils, and lymphocytes infiltrate into the nasal mucosa and release mediators that augment the allergic inflammatory reaction. Eosinophils are thought to be the most important cell in the late-phase reaction, releasing eosinophil cationic protein, major basic protein, eosinophil-derived neurotoxin, and additional inflammatory mediators such as leukotrienes. Any histamine present during the late-phase reaction is believed to come from basophils and not mast cells.[1] Symptoms include more persistent congestion and mucus secretion.

Because histamine is not the major mediator in the late-phase reaction, antihistamines are less effective in this period. Inhaled nasal corticosteroids have proven more effective than antihistamines for relief of late-phase reaction-induced congestion.

There may be some exceptions, however. The second-generation antihistamine cetirizine appears to inhibit infiltration of

TABLE 2

Metabolism, pharmacokinetics, and safety of second-generation antihistamines

DRUG	METABOLISM	TIME TO PEAK LEVEL (HOURS)	HALF LIFE (HOURS)	PROTEIN BINDING (%)	POTENTIAL FOR SEDATION	PREGNANCY CATEGORY
Acrivastine	67% excreted unchanged	1	2	50%	Sometimes	C†
Azelastine	P450 (isoform unknown)	2–3	22	88%	Sometimes	C†
Cetirizine	50% excreted unchanged	1	8	93%	Sometimes	B*
Fexofenadine	95% excreted unchanged	3	14	60%–70%	No	C†
Loratadine	P450 3A4 and P450 2D6	1	8–28‡	97%	No	B*

*B: Animal studies do not indicate a risk to the fetus and there are no controlled human studies, or animal studies do show an adverse effect on the fetus but well controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
†C: Studies have shown that the drug exerts animal teratogenic or embryocidal effects, but there are no controlled studies in women, or no studies are available in either animals or women.
‡Parent drug and active metabolites.

eosinophils, neutrophils, and basophils during the late-phase reaction, and may diminish the actions of other inflammatory mediators.[2–4] Azelastine has also demonstrated some novel antiallergic properties such as decreasing histamine release from mast cells, preventing activation of inflammatory cells, and inhibiting synthesis of leukotrienes.[5]

SAFETY OF SECOND-GENERATION ANTIHISTAMINES

Drug interactions and cardiotoxicity

Terfenadine (Seldane) and astemizole (Hismanal), the first nonsedating antihistamines approved in the United States, were recently withdrawn amid reports of QT prolongation, torsades de pointes,[6–8] and even deaths in persons taking these drugs.

The problem with these drugs was in their metabolism. The hepatic cytochrome P450 CYP3A4 system, which metabolizes terfenadine and astemizole, also metabolizes many other drugs such as imidazole antifungal agents (eg, ketoconazole) and macrolide antibiotics (eg, erythromycin).[9] Concomitant use of these drugs inhibits the P450 system and allows terfenadine or astemizole to accumulate to dangerously high levels, as does hepatic dysfunction and even grapefruit juice.[10] (At high levels, terfenadine blocks potassium channels and prolongs the QT interval; in addition, astemizole also has been shown to prolong the QT interval and has a particularly long half-life, making it difficult to reverse any cardiotoxic effects.)

In view of these effects, the newer agents have undergone more scrutiny for potential drug interactions and cardiac side effects, and they appear safe. Fexofenadine, a metabolite of terfenadine, undergoes very little hepatic metabolism, while the other new agents rely on the P450 system less than did terfenadine and astemizole or can be metabolized by more than one P450 isoenzyme (TABLE 2). While levels of loratadine and fexofenadine increase with concomitant use of drugs metabolized by cytochrome P450, there appear to be no associated clinical adverse effects.[11,12] No QT prolongation has been seen with high doses of fexofenadine.[13]

Acrivastine, azelastine, and cetirizine still produce some sedation

Sedation

Up to 25% of persons taking first-generation antihistamines experience sedation to some extent, and studies have linked the use of these agents to driving impairment, occupational accidents, and decreased learning in children.[14–17] In fact, the District of Columbia and 35 states have ordinances that prohibit

driving motor vehicles while under the influence of sedating substances, including first-generation antihistamines, and some of these agents carry warnings on their labels to avoid machine operation or automobile driving while using them.

Compared with first-generation antihistamines, the second-generation antihistamines produce less sedation, as their molecules are less lipophilic and therefore less likely to penetrate the blood-brain barrier. Three of them are not entirely free of this side effect, however.

Acrivastine and azelastine produce somnolence more frequently than does placebo.

Cetirizine also produces somnolence more frequently than does placebo (in 14% of patients vs 6%), although less often than with the first-generation antihistamine hydroxyzine. Some experts therefore consider cetirizine "low-sedating" rather than "nonsedating."[18] The effect appears to be dose-related.

The package inserts for acrivastine, azelastine, and cetirizine state "due caution should therefore be exercised when driving a car or operating potentially dangerous machinery. Concurrent use [of acrivastine, azelastine or cetirizine] with alcohol or other CNS depressants should be avoided because additional reductions in alertness and additional impairment of CNS performance may occur."

In common colds, most studies found antihistamines no better than placebo

Use in pregnancy

Antihistamines cross the placenta. Acrivastine, azelastine, and fexofenadine carry a pregnancy category C rating, while loratadine and cetirizine are rated as category B. (For definition of categories, see TABLE 2.)

Use in nursing mothers

Antihistamines are excreted in breast milk. Nursing infants whose mothers have taken first-generation antihistamines have been reported to become irritable and drowsy. There are no published studies on this effect with the second-generation antihistamines.

Carcinogenicity

In a provocative study, Brandes et al[19] found that daily injections of astemizole, hydroxyzine, or loratadine promoted tumor growth in mice that had previously received injections of tumor cells, whereas no effects were seen with cetirizine or doxylamine.

No other published studies corroborate these findings in mice or humans, and the FDA has not issued any new recommendations regarding the use of these medications. The FDA does not usually approve medications found to be carcinogenic in standard tests in rodents, and there are no retrospective data indicating that first-generation antihistamines may be carcinogenic.

Other effects

Compared with first-generation antihistamines, the newer agents cause fewer cholinergic, serotonergic, and dopaminergic effects.

RELATIVE EFFICACY OF SECOND-GENERATION ANTIHISTAMINES

Overall, the available second-generation antihistamines appear similar in their efficacy in relieving allergic rhinitis symptoms. Only a few studies have compared them head-to-head, however.

In one study,[20] 111 ragweed-sensitive patients received a controlled inhaled dose of ragweed pollen for 1 hour and then received one of five treatments: astemizole, cetirizine, loratadine, terfenadine, or placebo. The proportion of patients who obtained clinically significant relief ranged from 70% with cetirizine to 32% with placebo, but the differences were not significant. In addition, the times to onset of clinically important relief were not significantly different among the four groups receiving antihistamines.

Another study[21] compared the effects of astemizole, cetirizine, chlorpheniramine, loratadine, terfenadine, loratadine, and placebo on the surface areas of histamine-induced skin wheals and flares, a measurement used to demonstrate pharmacodynamic activity of antihistamines. The order of most effective to least effective was cetirizine 10 mg, terfenadine 120 mg, terfenadine 60 mg, loratadine 10 mg, astemizole 10 mg, and chlorpheniramine 4 mg. The differences between the medications were statistically significant ($P < .01$).

TABLE 3

Second-generation antihistamines: Dosage and administration in allergic rhinitis

DRUGS	TRADE NAME	DOSAGE
Acrivastine 8 mg with pseudoephedrine 60 mg†	Semprex-D capsules	Adults*: 1 capsule four times a day
Azelastine	Astelin nasal spray	Adults: two sprays in each nostril twice a day
Cetirizine	Zyrtec tablets and syrup	Adults and children 6 years and older: 5–10 mg daily Children 2–5 years: 2.5–5 mg daily Adults and children 6 years and older with renal failure: 5 mg daily
Fexofenadine	Allegra capsules	Adults: 60 mg twice a day In renal failure: 60 mg daily
Fexofenadine 60 mg with pseudoephedrine 120 mg†	Allegra D capsules	Adults: 60 mg twice a day In renal failure: 60 mg daily
Loratadine	Claritin tablets, syrup, and rapidly disintegrating tablets	Adults: 10 mg daily In hepatic or renal failure: 10 mg every other day
Loratadine 5 mg with pseudoephedrine 120 mg†	Claritin-D 12 Hour extended-release tablets	Adults: One tablet twice a day In renal failure: One tablet daily In hepatic failure: Avoid
Loratadine 10 mg with pseudoephedrine 240 mg†	Claritin-D 24 Hour extended-release tablets	Adults: One tablet daily

*12 years and older
†Pseudoephedrine can have side effects such as nervousness, tremor, and insomnia; use with caution in patients with hypertension, coronary artery disease, arrhythmias, hyperthyroidism, glaucoma, and urinary dysfunction

The effectiveness of antihistamines may be altered by the level of allergen exposure, the level of allergic sensitization, and whether allergic symptoms are present before using the drug. The choice of an antihistamine is based on its safety profile, individual incidence of adverse side effects, cost, compliance with dosing schedule, and patient preference.

CLINICAL INDICATIONS

Allergic rhinitis

Guidelines from the American College of Allergy, Asthma, and Immunology recommend second-generation antihistamines as first-line therapy for allergic rhinitis, in view of their safety and evidence that some of them may have antiasthma benefits.[22] All of them decrease sneezing, pruritus, and rhinorrhea, especially if taken before allergen exposure.

Preparations and dosages of second-generation antihistamines used in treating allergic rhinitis are listed in TABLE 3.

Additional medications for allergic rhinitis. Antihistamines are generally the first medications used for allergic rhinitis, either over-the counter preparations or prescribed second-generation formulations. If antihistamines do not provide enough relief, intranasal corticosteroids are often prescribed. These agents are highly effective in decreasing allergic symptoms of both the early-phase and late-phase reactions. Oral decongestants can reduce congestion associated with allergic rhinitis but can have significant side effects. Topical sympathomimetics are not recommended for use longer than 2 days. Other medications also used are intranasal cromolyn and intranasal ipratropium bromide.

TABLE 4

Costs of antihistamines and steroid nasal sprays

DRUG AND DOSAGE	WHOLESALE COST PER MONTH
First-generation antihistamines	
Chlorpheniramine (generic; 4 mg four times a day)	$1.24
(generic; extended-release capsules, 8 mg twice a day)	$13.72
Diphenhydramine (generic; 25 mg four times a day)	$1.58
Second-generation antihistamines	
Acrivastine (Semprex-D; 1 capsule four times a day)	$86.26
Azelastine (Astelin; two sprays each side twice a day)	$44.76
Cetirizine (Zyrtec; 5 or 10 mg daily	$55.80
Fexofenadine (Allegra; 60 mg twice a day)	$59.65
(Allegra D; 60 mg twice a day)	$66.60
Loratadine (Claritin; 10 mg daily)	$65.66
(Claritin D 12 Hour; 1 tablet twice a day)	$74.00
(Claritin D 24 Hour; 1 tablet daily)	$74.00
Nasal steroid sprays	
Beclomethasone dipropionate	
(Beconase AQ 1–2 sprays twice a day each side)	$21.46
(Vancenase AQ double strength one or two sprays each side twice a day)	$41.24
Budesonide (Rhinocort; two sprays each side twice a day)	$36.17
Fluticasone (Flonase two sprays each side daily)	$49.87
Triamcinolone (Nasacort AQ two sprays daily)	$40.67

DATA FROM RED BOOK. MONTVALE, NJ, MEDICAL ECONOMICS COMPANY, 1999.

Chronic idiopathic urticaria

Chronic idiopathic urticaria is defined as hives persisting longer than 6 weeks without a clear cause. Patients with urticaria may have mast cells that degranulate in response to several histamine-releasing factors. Therefore, antihistamines have been used in treating acute and chronic hives.

In this situation, sedation may be desirable, and some patients may prefer first-generation antihistamines precisely because of their sedative properties, especially for nighttime use.

The FDA has approved the use of loratadine and cetirizine for chronic idiopathic urticaria, and studies are underway with fexofenadine.

Anaphylaxis

The treatment of choice for anaphylaxis and anaphylactoid reactions is epinephrine, but antihistamines are beneficial in reversing the symptoms produced by histamine. Diphenhydramine and hydroxyzine are most frequently used because parenteral forms are available. None of the second-generation antihistamines are available for intravenous use at this time.

Asthma

Although anti-inflammatory medications—corticosteroids, nedocromil, cromolyn, and leukotriene antagonists—and bronchodilators are the primary agents used for treating asthma,[23] some studies indicate that the second-generation antihistamines may also be beneficial.[24–26] The anti-inflammatory effects of cetirizine may prove helpful for patients who have both allergic rhinitis and asthma.[27,28]

It is a mistaken belief that people with asthma cannot take antihistamines. The American Academy of Allergy and Immunology recommends that antihistamines not be withheld from patients with asthma who need them for concomitant diseases such as allergic rhinitis, allergic dermatoses, and

urticaria, unless a previous adverse reaction has occurred.[29]

Histamine is a known bronchoconstrictor, and increased levels are seen in allergen challenges as well as in nonspecific challenges with exercise and cold air. An estimated 60% to 80% of patients with allergic rhinitis develop bronchial hyperreactivity, and asthma is three to five times more likely to occur in persons with seasonal allergic rhinitis.[30]

The classic antihistamines are limited in their effectiveness against asthma owing to their anticholinergic and alpha-adrenergic effects. In addition, antiasthma benefits appear to be dose-related, and effects are generally seen at doses higher than usually indicated for the treatment of allergic rhinitis.

Additional studies are required to determine if nonsedating antihistamines are helpful for asthmatic patients without allergic rhinitis and if benefit can be attained at safe dosages.

Atopic dermatitis

No second-generation antihistamine has FDA approval for treating atopic dermatitis, but cetirizine[31] and loratadine[32] were more effective than placebo in decreasing the pruritus of atopic dermatitis in clinical trials. In this situation, however, first-generation antihistamines might be useful not only to relieve pruritus but also for sedation.

Upper respiratory infections

Antihistamines are frequently used to relieve nasal symptoms of viral upper respiratory infections, usually in combination with decongestants. Clemastine, a first-generation antihistamine, decreased sneezing, nasal secretions, and rhinorrhea in a study in patients inoculated by rhinovirus, and has FDA approval for use in colds.[33]

On the other hand, most studies found antihistamines (with or without decongestants) no better than placebo in relieving symptoms of the common cold.[34] There are no published studies regarding nonsedating antihistamines and the treatment of upper respiratory infections.

COST

Nonsedating antihistamines are more expensive than first-generation preparations (TABLE 4). Intranasal steroids are somewhat less costly than second-generation antihistamines. Cost may not be an issue if the patient has a prescription plan; however, many of these plans may restrict which antihistamines can be prescribed. If the physician recommends no substitution, additional costs may be passed on to the patient.

SUMMARY

Second-generation antihistamines are safe and effective medications for allergic conditions. Control of nasal congestion may require additional medication. Further studies will determine if nonsedating antihistamines can be utilized for other medical conditions.

REFERENCES

1. **Naclerio RM, Proud D, Togias AG, et al.** Inflammatory mediators in late antigen-induced rhinitis. N Engl J Med 1985; 313:65–70.
2. **Michel L, DeVos C, Dubertret L.** Cetirizine effects on cutaneous allergic reaction in humans. Ann Allergy 1990; 65:512–516.
3. **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; 90:215–224.
4. **Ciprandi G, Buscaglia S, Pesce G, et al.** Cetirizine 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; 95:612–621.
5. **Chand N, Sofia RD.** Azelastine—A novel in vivo inhibitor of leukotriene biosynthesis: A possible mechanism of action: A mini review. J Asthma 1995; 32:227–234.
6. **Monahan B, Ferguson C, Killeavy, E, Lloyd B, Troy J, Cantilena L.** Torsades de pointes occurring in association with terfenadine use. JAMA 1990; 264:2788–2790.
7. **Leor J, Harman M, Rabinowitz B, Mozes B.** Giant U waves and associated ventricular tachycardia complicating astemizole overdose: Successful therapy with intravenous magnesium. Am J Med 1991; 91:94–97.
8. **Wiley J, Gelber M, Henretig F, et al.** Clinical and laboratory observations, cardiotoxic effects of astemizole overdose in children. J Ped 1992; 120:799–802.
9. **Woosley R, Chen Y, Freiman J, Gillis R.** Mechanism of the cardiotoxic actions of terfenadine. JAMA 1993; 269:1532–1536.
10. **Benton RE, Honig PK, Zamani K, et al.** Grapefruit juice alters terfenadine pharmacokinetics, resulting in prolongation of repolarization on the electrocardiogram. Clin Pharmacol Ther 1996; 59:383–388.
11. **Tinkelman D, Falliers C, Bronsky E, et al.** Efficacy and safety of fexofenadine HCl in fall seasonal allergic rhinitis [abstract]. J Allergy Clin Immunol 1996; 97:435.
12. **Affrime MB, Lovber R, Danzig M, et al.** Three month evaluation of electrocardiographic effects of loratadine in humans [abstract]. J Allergy Clin Immunol 1993; 91:259.
13. **Russell T, Stoltz M, Weir S.** Pharmacokinetics, pharmacodynamics, and tolerance of single- and multiple-dose fexofenadine hydrochloride in healthy male volunteers. Clin Pharmacol Ther 1998; 64:612–621.

14. **Aso T, Sakai Y.** Effect of terfenadine, a novel antihistamine, on actual driving performance [abstract]. Ann Allergy 1989; 62:250.
15. **Gillmore TM, Alexander BH, Muller BA, et al.** Occupational injuries and medication use. Am J Ind Med 1996; 30:234–239.
16. **Vuurman EF, Van Veggel L, Uiterwijk MM, et al.** Seasonal allergic rhinitis and antihistamine effects on children's learning. Ann Allergy 1993; 71:121–126.
17. **Weiler JM, Bloomfield JR, Woodworth GG, et al.** Effects of fexofenadine, diphenhydramine, and alcohol on driving performance. A randomized, placebo-controlled trial in the Iowa driving simulator. Ann Intern Med 2000; 132:354–363.
18. **Nightingale CH.** Treating allergic rhinitis with second-generation antihistamines. Pharmacotherapy 1996; 16:905–914.
19. **Brandes LJ, Warrington RC, Arron RJ, et al.** Enhanced cancer growth in mice administered daily human equivalent dosed of some H_1 antihistamines: Predictive in vitro correlates. J Natl Cancer Inst 1994; 86:770–775.
20. **Day JH, Briscoe MP, Clark RH, Ellis AK, Gervais P.** Onset of action and efficacy of terfenadine, astemizole, cetirizine and loratadine for the relief of symptoms of allergic rhinitis. Ann Allergy 1997; 79:163–172.
21. **Simons FE, McMilan JL, Simons KJ.** A double-blind, single-dose, crossover comparison of cetirizine, terfenadine, loratadine, astemizole, and chlorpheniramine versus placebo: Suppressive effects on histamine-induced wheals and flares during 24 hours in normal subjects. J Allergy Clin Immunol 1990; 86:540–547.
22. **Dykewicz MS, Fineman S, Skoner DP, et al.** Diagnosis and management of rhinitis: Parameter documents of the Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology. Ann Allergy Asthma Immunol 1998; 81:478–518.
23. **National Asthma Education and Prevention Program.** Expert Panel Report II. Guidelines for the Diagnosis and Management of Asthma. Bethesda, MD: National Heart, Lung and Blood Institute and the National Institutes of Health, 1997.
24. **Rafferty P, Holgate ST.** Terfenadine (Seldane) is a potent and selective histamine H_1-receptor antagonist in asthmatic airways. Am Rev Respir Dis 1987; 135:181–184.
25. **Cistero A, Abadias M, Lieonaart R.** Effects of astemizole on allergic asthma. Ann Allergy 1992; 69:123–127.
26. **Corren J, Harns AG, Aaronson D, et al.** Efficacy and safety of loratadine plus pseudoephedrine in patients with seasonal allergic rhinitis and mild asthma. J Allergy Clin Immunol 1997; 100:781–788.
27. **Grant JA, Nicodemus CF, Findlay SR, et al.** Cetirizine in patients with seasonal rhinitis and concomitant asthma: prospective, randomized, placebo-controlled trial. J Allergy Clin Immunol 1995; 95:923–932.
28. **Spector SL, Nicodemus CF, Corren J, et al.** Comparison of the bronchodilatory effects of cetirizine, albuterol, and both together versus placebo in patients with mild-to-moderate asthma. J Clin Immunol 1995; 96:174–181.
29. **Sly RM, Kemp JP, Anderson JA, et al.** Position statement. The use of antihistamines in patients with asthma. J Allergy Clin Immunol 1988; 82:481–482
30. **Ledford DK, Lockey RF.** Allergic rhinitis: Offering relief this season. J Respir Dis 1998; 19:647–666.
31. **La Rosa M, Ranno C, Mussarra I, et al.** Double-blind study of cetirizine in atopic eczema in children. Ann Allergy 1994; 73:117–122.
32. **Langeland T, Fagertun HE, Larsen S.** Therapeutic effect of loratadine on pruritus in patients with atopic dermatitis. A multi-cross over designed study. Allergy 1994; 49:22–26.
33. **Gwaltney JM Jr, Park J, Paul RA, et al.** Randomized controlled trial of clemastine fumarate for treatment of experimental rhinovirus colds. Clin Infect Dis 1996; 22:656–662.
34. **Clemens CJ, Taylor JA, Almquist JR, et al.** Is an antihistamine-decongestant combination effective in temporarily relieving symptoms of the common cold in preschool children? J Ped 1997; 130:463–466.

ADDRESS: *Lily C. Pien, MD, Department of Allergy and Immunology, A72, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail pienl@ccf.org.*

In hypertension or angina...

Convenient once-daily dosing

The usual starting dose is 5 mg in hypertension or angina

—In hypertension, small, fragile, or elderly individuals, or patients with hepatic insufficiency may be started on 2.5 mg once daily

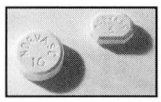
Titration can proceed to 10 mg

—Most angina patients will require 10 mg

Can be taken with or without food

An excellent side-effect profile

	DOSE-RELATED SIDE EFFECTS	NORVASC 5 mg (%) (N=296)	NORVASC 10 mg (%) (N=268)	PLACEBO (%) (N=520)
ADVERSE EVENT	Edema	3.0	10.8	0.6
	Dizziness	3.4	3.4	1.5
	Flushing	1.4	2.6	0.0
	Palpitation	1.4	4.5	0.6



Rx
Norvasc 5 mg
30
Sig: 1 tablet po daily

Once-Daily 5-mg and 10-mg tablets

NORVASC®
(amlodipine besylate)

The most prescribed cardiovascular agent in the world[4*]

***Among branded cardiovascular agents indicated for hypertension and/or angina.**[4]

References: 1. Velasco M, Urbina A, Silva H, et al. A double-blind, parallel, comparative evaluation of amlodipine vs. captopril in the monotherapeutic treatment of mild and moderate essential hypertension. *J Cardiovasc Pharmacol.* 1991;17(suppl 1):S19-S21. **2.** Kloner RA, Sowers JR, DiBona GF, Cobb M, Wein M, Gaffney M. Women have a higher response rate than men to the antihypertensive calcium channel blocker amlodipine. *J Am Coll Cardiol.* February 1995;32A. Abstract. **3.** Hayduk K, Adamczak M, Nowitzki G. Is initial dose titration of amlodipine worthwhile in patients with mild to moderate hypertension? *Curr Med Res Opin.* 1999;15:39-45. **4.** IMS International Prescription Data (based on 29 countries moving annual total), June 1999; IMS National Prescription Audit (total prescriptions), YTD October 1999.

Pharmaceutical Roundtable Member℠ A Partner in Research and Education

American Heart Association® Fighting Heart Disease and Stroke

Pfizer U.S. Pharmaceuticals

NC426A99

Brief Summary
NORVASC® (amlodipine besylate) Tablets
For Oral Use

CONTRAINDICATIONS: NORVASC is contraindicated in patients with known sensitivity to amlodipine.

WARNINGS: Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

PRECAUTIONS: General: Since the vasodilation induced by NORVASC is gradual in onset, acute hypotension has rarely been reported after oral administration of NORVASC. Nonetheless, caution should be exercised when administering NORVASC as with any other peripheral vasodilator particularly in patients with severe aortic stenosis.

Use in Patients with Congestive Heart Failure: In general, calcium channel blockers should be used with caution in patients with heart failure. NORVASC (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). NORVASC has been compared to placebo in four 8-12 week studies of patients with NYHA Class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

Beta-Blocker Withdrawal: NORVASC is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of the beta-blocker.

Patients with Hepatic Failure: Since NORVASC is extensively metabolized by the liver and the plasma elimination half-life (t ½) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering NORVASC to patients with severe hepatic impairment.

Drug Interactions: *In vitro* data in human plasma indicate that NORVASC has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin). Special studies have indicated that the co-administration of NORVASC with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers; that co-administration with cimetidine did not alter the pharmacokinetics of amlodipine; and that co-administration with warfarin did not change the warfarin prothrombin response time.

In clinical trials, NORVASC has been safely administered with thiazide diuretics, beta-blockers, angiotensin converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis), was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis).

Pregnancy Category C: No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats or rabbits were treated orally with up to 10 mg/kg amlodipine (respectively 8 times* and 23 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis) during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats administered 10 mg/kg amlodipine for 14 days before mating and throughout mating and gestation. Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while NORVASC is administered.

Pediatric Use: Safety and effectiveness of NORVASC in children have not been established.

ADVERSE REACTIONS: NORVASC has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with NORVASC was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with NORVASC were of mild or moderate severity. In controlled clinical trials directly comparing NORVASC (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of NORVASC due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effects which occurred in a dose related manner are as follows: edema (1.8% at 2.5 mg, 3.0% at 5.0 mg, and 10.8% at 10.0 mg, compared with 0.6% placebo); dizziness (1.1% at 2.5 mg, 3.4% at 5.0 mg, and 3.4% at 10.0 mg, compared with 1.5% placebo); flushing (0.7% at 2.5 mg, 1.4% at 5.0 mg, and 2.6% at 10.0 mg, compared with 0.0% placebo); and palpitation (0.7% at 2.5 mg, 1.4% at 5.0 mg, and 4.5% at 10.0 mg, compared with 0.6% placebo).

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following: headache (7.3%, compared with 7.8% placebo); fatigue (4.5%, compared with 2.8% placebo); nausea (2.9%, compared with 1.9% placebo); abdominal pain (1.6%, compared with 0.3% placebo); and somnolence (1.4%, compared with 0.6% placebo).

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as follows: edema (5.6% in men, 14.6% in women, compared with a placebo incidence in men of 1.4% and 5.1% in women); flushing (1.5% in men, 4.5% in women, compared with a placebo incidence of 0.3% in men and 0.9% in women); palpitations (1.4% in men, 3.3% in women, compared with a placebo incidence of 0.9% in men and 0.9% in women); and somnolence (1.3% in men, 1.6% in women, compared with a placebo incidence of 0.8% in men and 0.3% in women).

The following events occurred in ≤1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship: **cardiovascular:** arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension; **central and peripheral nervous system:** hypoesthesia, paresthesia, tremor, vertigo; **gastrointestinal:** anorexia, constipation, dyspepsia,** dysphagia, diarrhea, flatulence, vomiting, gingival hyperplasia; **general:** asthenia,** back pain, hot flushes, malaise, pain, rigors, weight gain; **musculo-skeletal system:** arthralgia, arthrosis, muscle cramps,** myalgia; **psychiatric:** sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization; **respiratory system:** dyspnea,** epistaxis; **skin and appendages:** pruritus,** rash,** rash erythematous, rash maculopapular; **special senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus; **urinary system:** micturition frequency, micturition disorder, nocturia; **autonomic nervous system:** dry mouth, sweating increased; **metabolic and nutritional:** thirst; **hemopoietic:** purpura.

The following events occurred in ≤0.1% of patients: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

NORVASC therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, creatinine or liver function tests.

NORVASC has been used safely in patients with chronic obstructive pulmonary disease, well compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

OVERDOSAGE: Single oral doses of 40 mg/kg and 100 mg/kg in mice and rats, respectively, caused deaths. A single oral dose of 4 mg/kg or higher in dogs caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of NORVASC is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg amlodipine and an unknown quantity of benzodiazepine in a suicide attempt, developed shock which was refractory to treatment and died the following day with abnormally high benzodiazepine plasma concentration. A case of accidental drug overdose has been documented in a 19 month old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine), should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit.

* Based on patient weight of 50 kg.

**These events occurred in less than 1% in placebo controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

More detailed professional information available on request.
Revised June 1996