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New products

Series editors: Donald Y. M. Leung, MD, PhD, Harold S. Nelson, MD, Stanley J. Szeffler, MD, Philip S. Norman, MD, and Andrea Apter, MD, MSc

Desloratadine: A new, nonsedating, oral antihistamine

Raif S. Geha, MD, and Eli O. Meltzer

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R.S.G. has received unrestricted research support to study desloratadine in immune systems. E.O.M. has conducted clinical studies with desloratadine.

This is a peer-reviewed invited article prepared on behalf of Schering-Plough by Raif S. Geha, MD, and Eli O. Meltzer, MD, with assistance from Charles Miller, MA, of ApotheCom Associates, LLC, Yardley, Pa.

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Desloratadine: A new, nonsedating, oral antihistamine

Raif S. Geha, MD,^a and Eli O. Meltzer, MD^b *Boston, Mass, and San Diego, Calif*

Desloratadine is a new, selective, H₁-receptor antagonist that also has anti-inflammatory activity. In vitro studies have shown that desloratadine inhibits the release or generation of multiple inflammatory mediators, including IL-4, IL-6, IL-8, IL-13, PGD₂, leukotriene C₄, tryptase, histamine, and the TNF- α -induced chemokine RANTES. Desloratadine also inhibits the induction of cell adhesion molecules, platelet-activating factor-induced eosinophil chemotaxis, TNF- α -induced eosinophil adhesion, and spontaneous and phorbol myristate acetate-induced superoxide generation in vitro. In animals desloratadine had no effect on the central nervous, cardiovascular, renal, or gastrointestinal systems. Desloratadine is rapidly absorbed, has dose-proportional pharmacokinetics, and has a half-life of 27 hours. The absorption of desloratadine is not affected by food, and the metabolism and elimination are not significantly affected by the subject's age, race, or sex. There are no clinically relevant interactions between desloratadine and erythromycin, ketoconazole, or grapefruit juice. Desloratadine is not a significant substrate of the P-glycoprotein transport system. Once daily administration of desloratadine rapidly reduces the nasal and nonnasal symptoms of seasonal allergic rhinitis, including congestion. In patients with seasonal allergic rhinitis and concomitant asthma, desloratadine treatment was also associated with significant reductions in total asthma symptom score and use of inhaled β_2 -agonists. Use of desloratadine in patients with chronic idiopathic urticaria was associated with significant reductions in pruritus, number of hives, size of the largest hive, and interference with sleep and daily activities. Clinical experience in over 2300 patients has shown that the adverse event profile of desloratadine is similar to that of placebo; desloratadine has no clinically relevant effects on electrocardiographic parameters, does not impair wakefulness or psychomotor performance, and does not exacerbate the psychomotor impairment associated with alcohol use. (*J Allergy Clin Immunol* 2001;107:751-62.)

Key words: Desloratadine, antihistamine, seasonal allergic rhinitis, asthma, urticaria, anti-inflammatory, drug interactions, safety, congestion

Abbreviations used

AUC:	Area under the plasma concentration-versus-time curve
CIU:	Chronic idiopathic urticaria
C _{max} :	Maximum plasma concentration
ED ₅₀ :	Median effective dose
OATP:	Organic anion transport polypeptide
P-gp:	P-glycoprotein
SAR:	Seasonal allergic rhinitis
TSS:	Total symptom score

RATIONALE FOR DRUG DEVELOPMENT

Allergic rhinitis is a common disease that affects up to 50 million Americans and up to 30% of the population in Europe.^{1,2} With the prevalence of the disease increasing, even greater numbers of the population will be affected in the future. Appropriate treatment is important to alleviate the signs and symptoms of allergic rhinitis, including sneezing, rhinorrhea, nasal congestion/stuffiness, and nasal pruritus, to improve patients' quality of life, and to facilitate the management of associated conditions, such as conjunctivitis, otitis media, sinusitis, and asthma.³

Antihistamines are a recommended first-line treatment for allergic rhinitis.³ Although there are many antihistamines from which to choose, none are ideal. The currently available antihistamines relieve most of the signs and symptoms of allergic rhinitis, but they are not considered to be very effective for the treatment of congestion.⁴ Consequently, antihistamines are often administered together with a decongestant to also reduce nasal obstruction.

Adverse event profiles also limit the use of many of the available antihistamines. Older antihistamines, such as diphenhydramine and chlorpheniramine, and, to a lesser extent, newer agents, such as cetirizine and azelastine, have been associated with sedation and psychomotor impairment.⁵⁻⁷ The newer antihistamines terfenadine and astemizole have been associated with prolongation of the QT_c interval and potentially fatal cardiac arrhythmias.⁸

Drug and food interactions also limit the use of many antihistamines. For example, plasma concentrations of terfenadine and astemizole may be increased when these agents are administered concomitantly with cytochrome P450 inhibitors, such as erythromycin and ketoconazole.⁸ This elevation of plasma levels is associated with an

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increased risk of cardiac adverse events. Other studies suggest that plasma levels of fexofenadine may be altered by means of concomitant administration of agents, such as erythromycin and ketoconazole, which are inhibitors or inducers of drug transporters, such as the organic anion transport polypeptide (OATP) or P-glycoprotein (P-gp).⁹ The maximum serum concentration of cetirizine is decreased when the product is administered with food.¹⁰

Desloratadine is a new antihistaminic compound currently under development (Fig 1). It is the primary active metabolite of loratadine. Early studies demonstrated that desloratadine is approximately 10 to 20 times more potent in H₁-receptor binding than loratadine in vitro and has 2.5 to 4 times more antihistaminic potency in animals.¹¹ Desloratadine was also shown to have a significantly longer half-life than loratadine.¹² A full-scale clinical development program has been conducted to investigate the efficacy and safety of desloratadine, and this article is a review of the data currently available.

PRECLINICAL PHARMACOLOGY

Antihistaminic activity

Desloratadine is an orally active H₁-receptor antagonist. In radioligand-receptor binding assays performed with isolated H₁ receptors from guinea pig lung and brain, desloratadine was 15 times more potent than loratadine and 10 to 20 times more potent than terfenadine in displacing tritiated mepyramine. Desloratadine was also 18 times more potent than loratadine in inhibiting tritiated pyrilamine binding to H₁ receptors isolated from rat brain. Functionally, desloratadine was approximately 10 times more potent than loratadine and terfenadine in inhibiting histamine-induced contractions in isolated guinea pig ileum.¹¹

Desloratadine potency was also demonstrated by using the human H₁ receptor cloned and expressed in Chinese hamster ovary cells. Desloratadine bound to the human H₁ receptor with 150- to 200-fold higher affinity compared with loratadine and fexofenadine, respectively (Table I).¹³ The antihistaminic potency of desloratadine was further demonstrated in several animal models. In the mouse desloratadine was approximately 4 times more potent than loratadine in inhibiting histamine-induced paw edema (median effective dose [ED₅₀] = 0.15 mg/kg vs 0.60 mg/kg, respectively; *P* < .05). Oral desloratadine protected guinea pigs from the lethal effects of histamine with a 2-fold lower ED₅₀ than loratadine (0.15 mg/kg vs 0.37 mg/kg, respectively). Topical desloratadine was approximately 10 times more potent than loratadine in inhibiting an increase in microvascular permeability in response to a histamine challenge to the upper airway of guinea pigs (ED₅₀ = 0.9 μg vs 8.7 μg, respectively).

Activity at other receptors

The high selectivity of desloratadine for the histamine receptor has been demonstrated in multiple studies. At concentrations of up to 10 μmol/L, desloratadine had no affinity for dopamine, monoamine oxidase, acetyl-

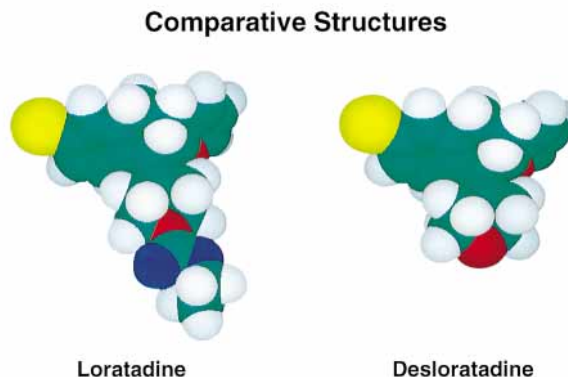


FIG 1. Space-filling model of the structures of loratadine and desloratadine.

TABLE I. Receptor-binding affinity of several histamine antagonists for the human H₁ receptor*

Compound	Displacement of tritiated pyrilamine (K _i , nmol/L)
Desloratadine	0.87 ± 0.08
Diphenhydramine	2.5 ± 0.2
Mizolastine	22 ± 5.9
Cetirizine	47.2 ± 10
Ebastine	51.7 ± 6.8
Loratadine	138 ± 23
Fexofenadine	175 ± 68

*Data on file, Schering-Plough.

cholinesterase, γ-amino butyric acid, or bradykinin receptors. Desloratadine had 15 to 50 times less affinity for the H₂ and muscarinic receptors than for the H₁ receptor. Desloratadine was substantially less potent than atropine in inhibiting acetylcholine-induced contractions in isolated guinea pig ileum and rat uterus. Furthermore, in an in vivo study in mice, desloratadine did not protect mice from death caused by the cholinergic agonist physostigmine.¹¹

Anti-inflammatory activity

In addition to the antihistaminic properties of desloratadine, in vitro studies have also shown that it has direct effects on inflammatory mediators, as illustrated in Fig 2. Schroeder et al¹⁴ demonstrated that desloratadine (100 nmol/L to 10 μmol/L) inhibits both IgE-mediated and non-IgE-mediated generation of the cytokines IL-4 and IL-13 by human basophils in vitro. Similarly, desloratadine (300 nmol/L to 100 μmol/L) inhibited both IgE and non-IgE-mediated histamine release from human peripheral blood basophils,¹⁵ and concentrations ranging from 10 fmol/L to 10 μmol/L inhibited the release of proinflammatory cytokines, such as IL-6 and IL-8, from basophils and mast cells.¹⁶

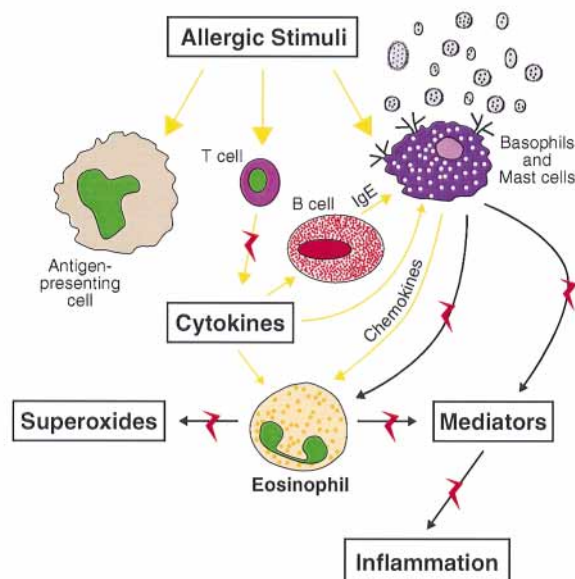


FIG 2. Diagram of the major pathways of allergic inflammation and potential sites for therapeutic intervention (blocked arrows) by an agent with both antiallergic and anti-inflammatory properties.

TABLE II. Steady-state pharmacokinetic values of desloratadine and 3-OH desloratadine after administration of 5 mg of desloratadine once daily for 10 days*

	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24} (ng · h ⁻¹ · mL ⁻¹)	Half-life (h)
Desloratadine	3.98	3.17	56.9	26.8
3-OH desloratadine	1.99	4.76	32.3	36.0

T_{max} , Time of maximum concentration.

*Data on file, Schering-Plough.

In human cells with high-affinity receptors for IgE (FcεRI), desloratadine (300 nmol/L to 100 μmol/L) reduced the release of PGD₂, leukotriene C₄, histamine, and tryptase¹⁵ and the TNF-α-induced chemokine RANTES. Desloratadine (10⁻⁵ mol/L) also inhibited the induction of cell adhesion molecules, such as intracellular adhesion molecule 1, in human nasal epithelial cells.¹⁷ These studies suggest that the anti-inflammatory effects of desloratadine are distinct from its activity as an H₁-receptor antagonist.

Desloratadine (10⁻⁷ mol/L to 10⁻⁵ mol/L) was also shown to inhibit platelet-activating factor-induced eosinophil chemotaxis and TNF-α-induced eosinophil adhesion in a study in which the eosinophils were obtained from patients with allergic rhinitis or allergic asthma. In addition, desloratadine significantly inhibited spontaneous and phorbol myristate acetate-induced superoxide generation.¹⁸ As with most studies of this type, the desloratadine concentrations used in these in vitro experiments range from therapeutic to supratherapeutic, and the concentrations of the challenge stimuli were likewise often higher

than those seen in vivo. Regardless, the mechanism by which desloratadine exerts these anti-inflammatory effects is independent of H₁-receptor antagonism, and it is reasonable to consider the observations from these studies to be relevant to clinical use.

Additional animal studies also confirm the beneficial effects of desloratadine. Desloratadine inhibited cough caused by aerosolized ovalbumin in sensitized guinea pigs; the minimum effective antitussive dose of desloratadine was 0.3 mg/kg, and that of loratadine was 1 mg/kg. In naturally allergic monkeys, desloratadine significantly inhibited bronchospasm in response to an antigen challenge.¹¹

Central nervous system effects

Studies in several animal models developed to assess the sedative liability of antihistamines demonstrated that desloratadine has no adverse effects on the central nervous system.¹⁹ In mice desloratadine doses of up to 300 mg/kg were not associated with decreased motor activity, decreased muscle tone, tremors-convulsions, ataxia, or lethality.²⁰ In addition, 160 mg/kg of desloratadine did not protect mice against electroconvulsive shock, inhibited acetic acid-induced writhing at a dose approximately 1000 times the antihistaminic dose,²⁰ and afforded no protection against physostigmine lethality at doses of up to 300 mg/kg.¹¹ Desloratadine doses of up to 12 mg/kg had no significant behavioral, neurologic, or autonomic effects in the rat.²⁰ The finding that intraperitoneal administration of desloratadine to guinea pigs did not inhibit in vitro binding of tritiated mepyramine to brain H₁ receptors suggests that desloratadine has no significant access to brain H₁ receptors.²⁰

Cardiovascular system effects

Data from animal studies indicate that desloratadine also has no effect on the cardiovascular system. An in vitro study demonstrated that desloratadine had no effects on the human-ether-a-go-go channel. The arrhythmias associated with terfenadine appear to result from terfenadine blockade of the human-ether-a-go-go channel.²⁰ When 4 mg/kg and 12 mg/kg oral doses of desloratadine were administered to rats, no effects on blood pressure were observed, and there were no significant electrocardiographic changes, including PR, QRS, and QT_c intervals.²⁰ Similarly, administration of a 25 mg/kg intravenous dose of desloratadine to guinea pigs resulted in no significant changes in blood pressure, heart rate, or QT_c, PR, or QRS intervals. In addition, a 12 mg/kg oral dose of desloratadine did not induce any significant ECG changes in monkeys.²⁰

Renal and gastrointestinal system effects

Pharmacologic studies in rats have also demonstrated that desloratadine does not adversely affect urine volume, electrolytes, or creatinine clearance. In addition, desloratadine did not inhibit gastric emptying or intestinal transit and did not have any harmful effects on the gastric mucosa of rats.²⁰

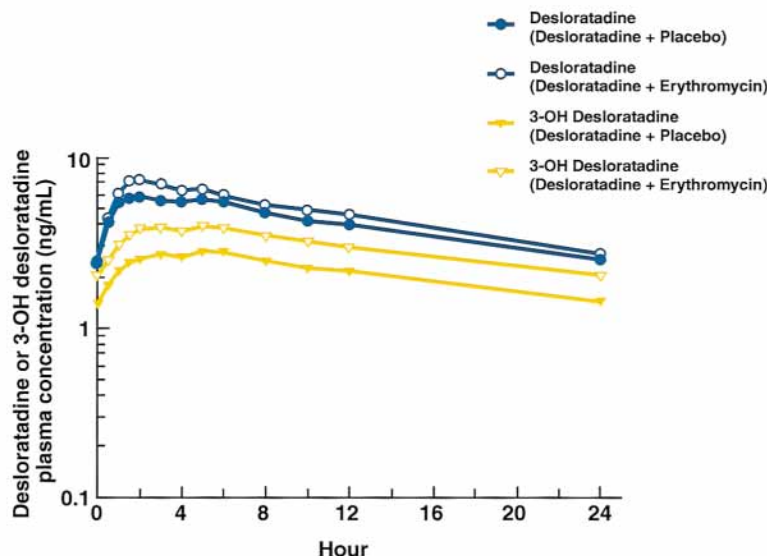


FIG 3. Mean plasma desloratadine and 3-OH desloratadine concentrations on day 10 after oral administration of 7.5 mg of desloratadine with erythromycin or with placebo. (Adapted with permission from Banfield C et al. Clin Pharmacokinet. In press.)

CLINICAL PHARMACOKINETICS

The pharmacokinetic properties of desloratadine have been studied in single- and multiple-dose trials, which demonstrated that desloratadine is rapidly absorbed and has a long half-life of approximately 27 hours. With daily administration of 5 mg of desloratadine, steady-state serum concentrations are achieved within 7 days. The steady-state pharmacokinetic parameters of desloratadine and its main metabolite, 3-OH desloratadine, are provided in Table II. Desloratadine has dose-proportional pharmacokinetics; both the maximum plasma concentration (C_{max}) and the area under the plasma concentration-versus-time curve (AUC) increase in a linear dose-proportional manner over the dose range of 5 mg to 20 mg.²¹ Maximum plasma concentrations of 2.18, 3.03, 3.80, and 8.08 ng/L were observed after administration of single oral doses of 5, 7.5, 10, and 20 mg, respectively.²¹ The AUC and C_{max} of a single 7.5-mg dose of desloratadine were similar after a 10-hour fast or immediately after a high-fat, high-calorie meal. Because the bioavailability and absorption of desloratadine are not significantly affected by food, desloratadine may be administered with or without meals.²²

The metabolite profiles of desloratadine in plasma, urine, and feces show that 3-OH desloratadine formation, and subsequent glucuronidation, is the major pathway of desloratadine metabolism. Three other hydroxylated metabolites each account for less than 6% of the excreted dose. Desloratadine has 6 fewer metabolites than loratadine (data on file, Schering-Plough).

Drug interactions—Alterations of drug metabolism

Thorough assessment of potential drug interactions has been a critical element of the evaluation of nonsedating antihistamines since the discovery of the potentially fatal interaction between terfenadine and the cytochrome P450 3A4 inhibitors erythromycin and ketoconazole. The results of electrocardiographic studies have revealed no clinically relevant interactions between desloratadine and erythromycin or ketoconazole. In a randomized, third-party, blind, crossover study, there were no clinically relevant or statistically significant differences between groups in change in ventricular rate or QT, PR, QRS, or QT_c intervals when subjects received 7.5 mg of desloratadine once daily for 10 days in combination with either placebo or 500 mg of erythromycin every 8 hours.²³ Concomitant administration of desloratadine with erythromycin resulted in only a slight clinically insignificant increase in the C_{max} and AUC₀₋₂₄ of desloratadine (1.2-fold and 1.1-fold, respectively; Fig 3) and 3-OH desloratadine (1.4-fold increases).

In a similarly designed study, subjects received 7.5 mg of desloratadine once daily along with 200 mg of ketoconazole every 12 hours or placebo for 10 days.²⁴ The combination of desloratadine and ketoconazole was not associated with any clinically relevant changes in QT, PR, QRS, or QT_c intervals. The observed change in ventricular rate among subjects receiving desloratadine and ketoconazole (5.6 beats/min) was less than the 12.2 beats/min change observed among subjects receiving

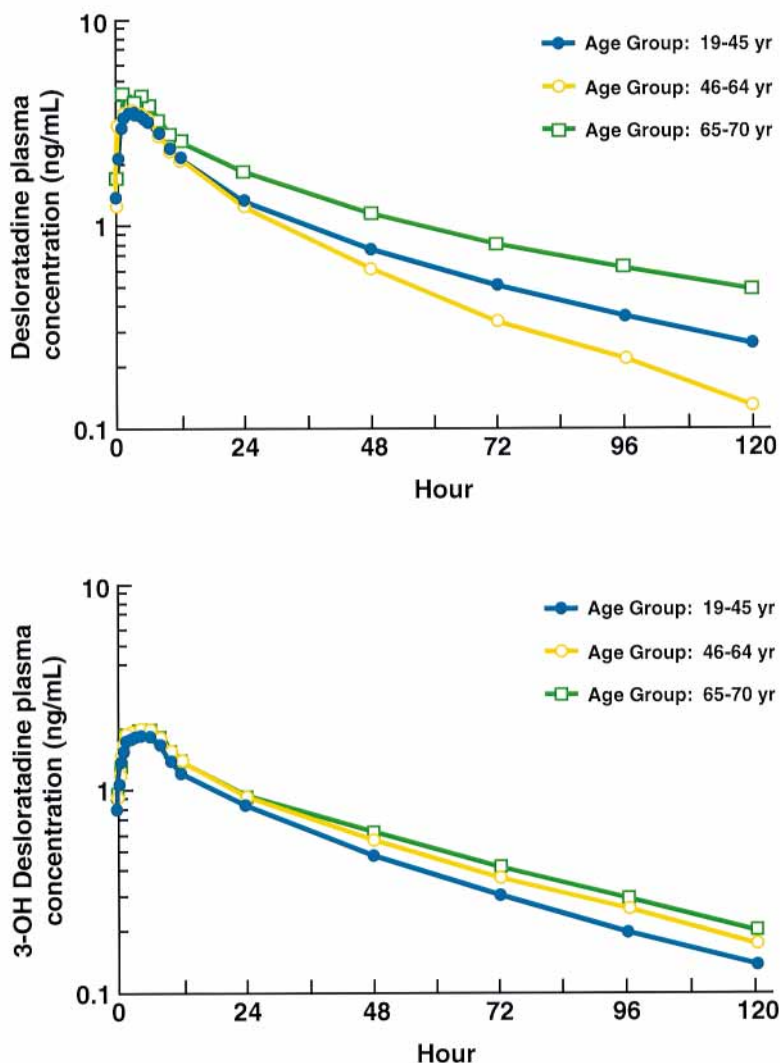


FIG 4. Mean concentration-time profiles for desloratadine (*top*) and 3-OH desloratadine (*bottom*) in 3 age groups after daily oral administration of 5 mg of desloratadine for 10 days. (Adapted with permission from Affrime M et al. Clin Pharmacokinet. In press.)

desloratadine and placebo. Concomitant administration of desloratadine and ketoconazole resulted in minimal accumulation of desloratadine (~1.3-fold increase) and 3-OH desloratadine (~1.5-fold increase).²⁴

Drug interactions—Alterations of drug uptake and elimination

Although many drug interactions are mediated wholly or in part by effects on cytochrome P450-mediated drug metabolism, recent research has identified a family of active drug transporters that are also critical targets for drug interactions. These transporters, which include P-gp and OATP, actively pump drugs and other substances across cell membranes and hence play an important role in determining an agent's pharmacokinetics. The P-gp transporter,

for example, is prevalent in the gastrointestinal tract, liver, blood-brain barrier, adrenal glands, and kidneys and acts as an efflux pump, removing foreign substances, including a wide variety of common drugs, from cells.²⁵⁻²⁷

The pharmacokinetics of some antihistamines, such as fexofenadine, can be altered by the induction or inhibition of these transporters.⁹ Cayen et al²⁸ demonstrated that desloratadine is not a significant substrate of P-gp. Desloratadine is therefore unlikely to have significant interactions with drugs that interact with the P-gp system, such as cyclosporine, ketoconazole, and erythromycin. The functioning of these active transporters can also be altered by compounds found in herbal remedies or foods, such as St John's wort, grapefruit juice, and red wine, raising the possibility of potential adverse interactions.²⁹

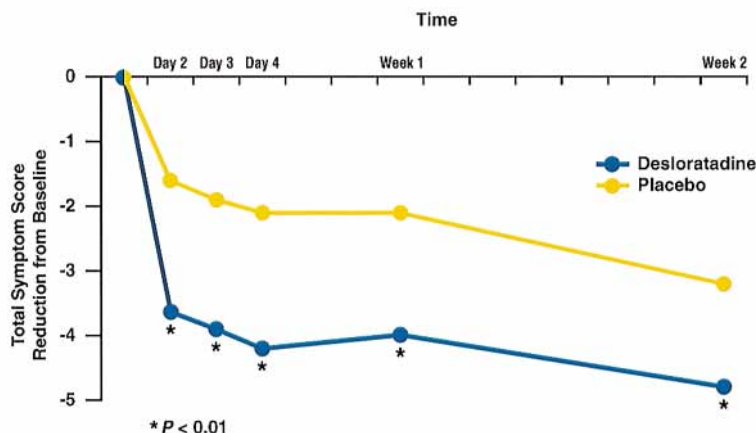


FIG 5. Time course for reduction in SAR total symptom scores (average reflective 12-hour morning/evening TSS) for 5 mg of desloratadine and placebo. Mean baseline scores for the desloratadine and placebo groups were 14.2 and 13.7, respectively. (Adapted with permission from Meltzer EO, et al. Clin Drug Invest 2001;21:25-32.)

For example, grapefruit juice can activate transporter systems (P-gp, OATP, or both) and thereby affect the serum concentrations of drugs that are transporter substrates. When healthy subjects were administered single 60-mg doses of fexofenadine with grapefruit juice, the rate (C_{max}) and extent of absorption (AUC) of fexofenadine were decreased by approximately 30% compared with that of fexofenadine administered with placebo. However, there was no statistically significant difference in the C_{max} or AUC of desloratadine or 3-OH desloratadine when the same subjects were administered single doses (5 mg) of desloratadine with or without grapefruit juice.³⁰

Pharmacokinetics of desloratadine in special populations

Results from clinical pharmacokinetic studies revealed no significant differences in the metabolism and elimination of desloratadine on the basis of a subject's age, race, or sex. There were no clinically relevant differences between groups in the multiple-dose pharmacokinetic parameters of desloratadine when subjects were stratified into 3 age groups (19-45, 46-64, and 65-70 years; Fig 4). Compared with subjects less than 65 years old, the C_{max} and AUC were 20% greater in the 65- to 70-year-old group, and the mean elimination half-life was 30% longer. These differences were not considered clinically important. No dosage adjustment of desloratadine is required in elderly subjects.¹² Similarly, single- and multiple-dose studies demonstrated no clinically relevant differences in the pharmacokinetic profiles of desloratadine and 3-OH desloratadine among men and women or among subjects of different races.³¹ Therefore no dosage adjustment of desloratadine is required on the basis of race or sex.

In patients with severe renal dysfunction (creatinine clearance, 5-29 mL $\cdot$ min⁻¹ $\cdot$ 1.73 m⁻²) or in those who were hemodialysis dependent, desloratadine C_{max} and

AUC values increased by approximately 1.7- and 2.5-fold, respectively. Patients with severe hepatic impairment, as defined by the Child-Pugh classification of hepatic dysfunction, had an apparent oral clearance of 28% of that found in normal subjects and a 2.4-fold increase in AUC compared with that found in normal subjects. There were no adverse events reported in either study. Since these levels are well below the patient exposure in studies with doses as high as 45 mg (see below), there is no anticipated safety risk (data on file, Schering-Plough).

EFFICACY IN PATIENTS WITH SEASONAL ALLERGIC RHINITIS

Multiple studies have demonstrated the efficacy of desloratadine in the treatment of seasonal allergic rhinitis (SAR). One set of efficacy evaluations was used consistently in all of the studies. Twice daily (once in the morning, immediately before study drug administration, and once in the evening, approximately 12 hours later), patients assessed nasal symptoms (rhinorrhea, nasal congestion/stuffiness, nasal itching, and sneezing) and non-nasal symptoms (itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears or palate). All symptoms were scored for reflective (how the patient felt in the preceding 12 hours) and instantaneous assessments (how the patient felt at the time of assessment). The mean morning/evening reflective assessments provided information on the effectiveness of therapy over an entire day, whereas the morning instantaneous assessments were analyzed to evaluate efficacy at the end of the 24-hour dosing interval. Symptoms were assessed by using a 4-point scale (0, none; 1, mild; 2, moderate; and 3, severe), and the individual nasal and nonnasal symptom scores were summed as a total symptom score (TSS). The primary endpoint was the 2-week average change from baseline in morning/evening reflective TSS.

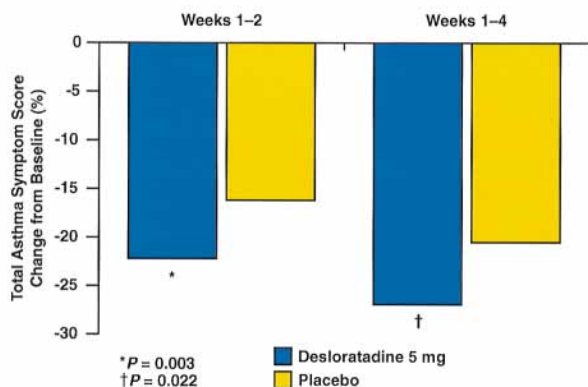


FIG 6. Change from baseline in total asthma symptom scores for 5 mg of desloratadine and placebo during weeks 1 to 2 and weeks 1 to 4.

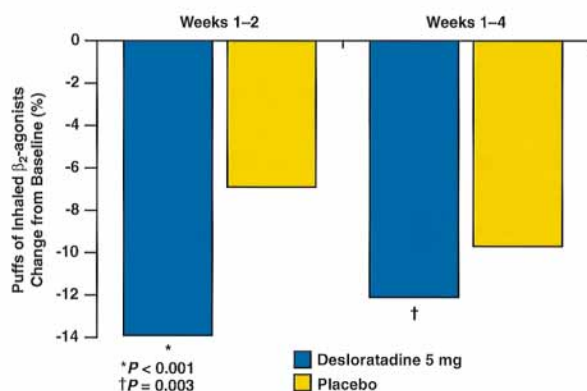


FIG 7. Change from baseline in use of inhaled β_2 -agonists for 5 mg of desloratadine and placebo during weeks 1 to 2 and weeks 1 to 4.

Two multicenter, randomized, double-blind studies compared the efficacy of desloratadine and placebo in patients who had a baseline TSS indicating moderate-to-severe SAR symptoms. In the first study a total of 346 patients (aged ≥ 12 years) received either 5 mg of desloratadine or placebo. The desloratadine group had a 28% reduction from baseline in the morning/evening reflective TSS, which was statistically significant ($P < .01$) when compared with the 13% reduction in the placebo group. Compared with placebo, the reduction in TSS in the group receiving 5 mg of desloratadine was statistically significant at the first complete efficacy evaluation on day 2 ($P < .01$, Fig 5). These effects were sustained throughout the 2-week study period. Furthermore, patients who received desloratadine had a significantly greater reduction in morning instantaneous TSS after only one dose of study medication than patients who received placebo (19% vs 2%, $P < .01$).³²

Similar findings were observed in the second study, in which 328 patients received 5 mg of desloratadine or

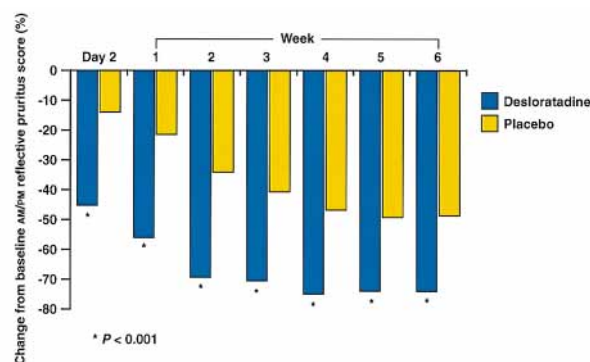


FIG 8. Change from baseline morning/evening reflective pruritus score in patients with CIU. Least-square mean baseline scores for desloratadine and placebo groups were 2.24 and 2.22, respectively. (Adapted with permission from Ring J. *Int J Dermatol* 2001; 40:1-5.)

placebo. Desloratadine therapy was associated with a significantly greater reduction from baseline in the 24-hour morning/evening reflective TSS over the 2 weeks of the study (30% vs 22%, $P = .02$ vs placebo).³² Taken together, these data demonstrate the rapid onset of action and sustained efficacy of desloratadine in patients with SAR.

EFFICACY IN PATIENTS WITH NASAL CONGESTION

Several studies have shown that therapy with once daily desloratadine significantly improves nasal congestion.³³ Relief of nasal congestion was examined in 3 multicenter, double-blind, placebo-controlled studies involving 278 to 346 patients with clinically symptomatic SAR. The endpoint for assessment of nasal congestion/stuffiness was the mean change from baseline in the morning/evening reflective congestion score averaged over the duration of the study, either 2 or 4 weeks. Baseline values in these studies ranged from 2.20 to 2.39 (symptom score: 0, none; 1, mild; 2, moderate; and 3, severe). The groups treated with 5 mg of desloratadine experienced a reduction in nasal congestion/stuffiness scores of 0.50 to 0.56 (21.3%-23.5%) from baseline. This effect was significant when compared with that found in the placebo groups, which experienced a decrease of 0.35 to 0.40 (13.6%-16.2%) from baseline ($P < .05$ for each study).

EFFICACY IN PATIENTS WITH CONCOMITANT SEASONAL ALLERGIC RHINITIS AND ASTHMA

Allergic rhinitis has been associated with asthma: up to 58% of patients with allergic rhinitis also have asthma.³⁴ A number of studies have demonstrated that appropriate management of allergic rhinitis in patients with asthma also results in improvement of asthma symptoms, decreased bronchial sensitivity, protection against bronchospasm, and decreased use of asthma rescue medica-

TABLE III. Incidence of treatment-emergent adverse events reported by 5% or more of the subjects in any treatment group by body system/organ class (all randomized subjects)*

	No.† (%) of subjects			
	Fall study		Spring study	
	Desloratadine, 5 mg (n = 164)	Placebo (n = 164)	Desloratadine, 5 mg (n = 172)	Placebo (n = 174)
No. of subjects (%) with any adverse events‡	81 (49)	85 (52)	69 (40)	64 (37)
Headache	40 (24)	44 (27)	28 (16)	25 (14)
Pharyngitis	11 (7)	5 (3)	6 (3)	3 (2)
Mouth dry	8 (5)	2 (1)	5 (3)	3 (2)
Dysmenorrhea	7 (6)	8 (7)	0 (0)	2 (2)
Somnolence	3 (2)	3 (2)	5 (3)	4 (2)

*Reprinted with permission from Meltzer EO et al. Clin Drug Invest 2001;21:25-32.

†Number of subjects reporting adverse events at least once during the study. Some subjects may have reported more than one adverse event.

‡Includes all treatment and emergent adverse events reported, without regard to relationship to treatment.

tions.^{3,4,34,35} Furthermore, it has been suggested that optimal control of asthma may require effective control of concomitant allergic rhinitis.³

Two 4-week, multicenter, double-blind studies have examined the use of desloratadine or placebo in 607 patients with at least a 2-year history of SAR and mild or moderate asthma. Study participants had symptoms of SAR and asthma for 3 days before baseline assessment, an FEV₁ of 70% to 100% of predicted value, and asthma symptoms controlled by using inhaled bronchodilators only. SAR symptoms were assessed as described previously in the SAR-only studies, and reflective and instantaneous assessments of asthma symptoms were also recorded twice daily. In addition, patients recorded their use of inhaled β_2 -agonists.^{36,37}

Ratner et al³⁷ described improvements in asthma symptoms and bronchodilator use in a pooled analysis of both studies. Compared with placebo, desloratadine treatment was associated with a significant decrease from baseline in the average total asthma symptom score after the first dose, an effect that was maintained over weeks 1 to 2 and 1 to 4 (Fig 6). Compared with placebo, desloratadine therapy was also associated with a statistically significant reduction in the use of inhaled β_2 -agonists over weeks 1 to 2 and 1 to 4 (Fig 7).³⁷

EFFICACY IN PATIENTS WITH CHRONIC IDIOPATHIC URTICARIA

Desloratadine has also been evaluated for the treatment of chronic idiopathic urticaria (CIU), another common condition in which antihistamines are first-line agents. In a multicenter, randomized, double-blind study, 190 patients 12 years of age or older with at least a 6-week history of CIU and who were experiencing a flare of at least moderate severity were randomized to treatment with 5 mg of desloratadine once daily or placebo

for 6 weeks. Twice daily, patients evaluated the severity of CIU symptoms (pruritus, number of hives, and size of the largest hive) over the previous 12 hours (reflective) and at the time of assessment (instantaneous) by using 4-point scales. As in the SAR studies, the individual symptom scores were summed for the TSS. Interference with sleep and interference with daily activities were also assessed by the patients, whereas patients and investigators jointly assessed CIU severity and therapeutic response.³⁸

Desloratadine was associated with a significantly greater reduction from baseline than placebo (Fig 8) for the primary endpoint, the average morning/evening reflective pruritus score over the first 7 days of treatment (56% vs 21.5%, $P < .001$). The benefits of desloratadine were noted at the first assessment, approximately 12 hours after administration of the first dose, and were maintained throughout the 6-week study. In addition, 24 hours after the first dose of study medication, desloratadine-treated patients had a significantly greater reduction from baseline in morning instantaneous pruritus score than that found in placebo-treated patients (45.1% vs 3.5%, $P < .001$). This effect was also maintained throughout the 6-week study.³⁸

Patients treated with desloratadine also had significantly greater reductions in morning/evening reflective and morning instantaneous TSS than those found in placebo-treated patients after the first dose, as well as throughout the 6 weeks of the study. Furthermore, patients receiving desloratadine treatment experienced significantly less interference with sleep and daily activities, beginning with the first dose. This effect was maintained throughout the entire 6-week study. Desloratadine-treated patients also had significantly greater decreases than did placebo-treated patients in the average morning/evening reflective and instantaneous assessments of the number of hives and the size of the largest hive over the first week of therapy, as well as over the entire study period ($P < .05$ for all evaluations). Through-

out the study, patients and investigators rated the overall condition of CIU and therapeutic response as being better in the desloratadine group.³⁸

ADVERSE EFFECTS

The overall adverse event profile for desloratadine is similar to that of placebo, as shown in 2 large studies conducted during the spring and fall allergy seasons (Table III).³² The most frequently observed adverse event in clinical studies was headache, which occurred at a similar rate with placebo and desloratadine treatment. Most adverse events reported in clinical studies were mild to moderate in severity. In studies using various doses of desloratadine (5-20 mg once daily), the number of subjects reporting adverse events was no different for any of the treatment doses (data on file, Schering-Plough). There were no differences in adverse events in young versus elderly, black versus white, or male versus female patients.^{12,31} No clinically significant effects on vital signs or laboratory tests in any studies have been reported to date.

Cardiovascular effects

Because the antihistamines terfenadine and astemizole have been associated with prolongation of the QT_c interval and fatal cardiac arrhythmias, it is important to discern the cardiac safety of all new antihistamines. In all clinical studies to date, desloratadine has had no clinically relevant effects on electrocardiographic parameters. The cardiac safety of desloratadine is further supported by a randomized double-blind study in which 24 healthy volunteers received 45 mg of desloratadine (9 times the 5-mg clinical dose) or placebo for 10 days and were then crossed over to the alternative treatment after a 14-day washout period. The maximum QT_c interval was comparable with desloratadine and placebo (429 and 433 ms, respectively). There were no differences between treatments in PR or QRS intervals, and the QT interval was shorter with desloratadine than with placebo. The difference between treatment groups in mean change from baseline ventricular rate was increased by 9.4 beats/min in the desloratadine group ($P < .01$); this was due to a single isolated heart rate of 117 beats/min with desloratadine and 112 beats/min with placebo and was of no clinical concern. Moreover, the estimated slope from regression analysis (mixed model) of the change from baseline for ventricular rate and plasma desloratadine plasma concentration was nearly zero (0.06), demonstrating the absence of a clinically relevant correlation between the ventricular rate and plasma desloratadine concentrations (data on file, Schering-Plough).

Central nervous system effects

Sedation is associated with older antihistamines and has also been noted with the use of cetirizine and azelastine.^{5,7} Coadministration of these products with alcohol can further impair psychomotor performance.⁵ Desloratadine, in contrast, does not impair wakefulness or psychomotor performance and does not exacerbate the psy-

chomotor impairment associated with alcohol use. In 2 randomized crossover studies,³⁹ a total of 44 healthy volunteers received single doses of 7.5 mg of desloratadine, 50 mg of diphenhydramine, and placebo to assess the effects of treatment on measures of sleepiness. The treatments were separated by 5-day washout periods. One study ($n = 20$) demonstrated that there was no difference between desloratadine and placebo on the basis of the Maintenance of Wakefulness Test (which measures the ability to stay awake), whereas the other ($n = 24$) demonstrated that there was no difference between desloratadine and placebo for the Multiple Sleep Latency Test (which measures the time to fall asleep). Both studies also demonstrated that there were no differences between desloratadine and placebo on the basis of psychomotor performance tests. As expected, both studies demonstrated statistically significant differences between diphenhydramine and both desloratadine and placebo for wakefulness, somnolence, and psychomotor tests ($P \leq .01$).³⁹

The potential for performance impairment with desloratadine was also assessed by Vuurman et al,⁴⁰ who demonstrated that desloratadine does not impair actual driving performance during an over-the-road driving test. In a randomized, 3-way, crossover study 18 healthy volunteers received single doses of 5 mg of desloratadine, 50 mg of diphenhydramine, and placebo (there was at least a 5-day washout period between each treatment). Unlike diphenhydramine, which was associated with significantly increased car weaving, reduced brake reaction time, and poorer scores on the car-following test when compared with placebo, desloratadine was not associated with any performance impairment.⁴⁰

The potential for exacerbation of alcohol effects by desloratadine was evaluated in a placebo-controlled, randomized, 4-way, crossover study with desloratadine at 7.5 mg, 50% higher than the recommended dose. There was no significant difference between desloratadine and placebo when administered with alcohol in standardized performance measures.⁴¹

CLINICAL APPLICATIONS

Dosage and administration

Various clinical studies have demonstrated that the long half-life of desloratadine allows once daily dosing. A 5-mg once daily dose is appropriate for treatment of both SAR and CIU. Because the pharmacokinetic parameters of desloratadine are not altered by subject race, sex, or age, no dosage adjustments are required on the basis of these factors for patients 12 years of age or older. Dosage adjustment is also not required if desloratadine is administered concomitantly with ketoconazole, erythromycin, or grapefruit juice. Furthermore, because the absorption of desloratadine is not affected by food, desloratadine may be administered with or without meals.

Place in therapy

Desloratadine has demonstrated relief of both the nasal (rhinorrhea, congestion, itching, and sneezing) and

nonnasal symptoms (itching/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears or palate) associated with allergic inflammatory reactions in patients 12 years of age and older. On the basis of the available efficacy and safety data and its convenient dosing regimen, desloratadine can be considered as a first-line treatment for patients with SAR. Desloratadine provides 24-hour relief of the signs and symptoms of SAR. Although there are safety concerns with many other antihistamines, desloratadine has a placebo-like adverse event profile and a clean drug-interaction profile.

SUMMARY

Allergic rhinitis is a common disease that is associated with substantial morbidity. Although there are many treatments available for the disease, none are ideal. There continues to be a need for treatments that relieve all of the signs and symptoms of the disease, do not cause adverse effects, do not have drug or food interactions, and can be conveniently administered.

Desloratadine is a new antihistamine that binds with higher affinity to the H₁ receptor than most other H₁-receptor antagonists. Desloratadine has also been shown to have anti-inflammatory properties *in vitro*. Preclinical studies have shown that desloratadine has no adverse effects on the central nervous, cardiovascular, or gastrointestinal systems. Desloratadine has no significant drug interactions, and its absorption is not affected by food. Because the pharmacokinetic profile does not vary with age, race, or sex in patients 12 years of age or older, there is no need to adjust the dose of desloratadine for these factors. Once daily administration of desloratadine improves nasal and nonnasal signs and symptoms of SAR, including a consistent improvement in nasal congestion. Desloratadine also improves SAR and asthma symptoms in patients with these comorbidities and provides relief for patients with CIU. When used in the treatment of SAR, SAR and asthma, or CIU, desloratadine has an adverse event profile similar to that of placebo. Unlike many antihistamines, desloratadine does not impair wakefulness, psychomotor function, or driving performance and does not exacerbate the effects of alcohol. Desloratadine also does not have adverse cardiovascular effects. On the basis of these preclinical and clinical studies of safety and efficacy, desloratadine appears to be a valuable new addition to the armamentarium of treatments for allergic diseases. Future evaluations will further clarify its place in the management of these prevalent and troublesome diseases.

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