

The pharmacologic profile of desloratadine: a review

Desloratadine is a new agent for the treatment of diseases such as seasonal allergic rhinitis and chronic urticaria. The pharmacologic profile of desloratadine offers particular benefits in terms of histamine H₁-receptor binding potency and H₁ selectivity. Desloratadine has a half-life of 21–24 h, permitting once-daily dosing. No specific cautions are required with respect to administration in renal or hepatic failure, and food or grapefruit juice have no effect on the pharmacologic parameters. No clinically relevant racial or sex variations in the disposition of desloratadine have been noted. In combination with the cytochrome P450 inhibitors, ketoconazole and erythromycin, the AUC and C_{max} of desloratadine were increased to a small extent, but no clinically relevant drug accumulation occurred. With high-dose treatment (45 mg/day for 10 days), no significant adverse events were observed, despite the sustained elevation of plasma desloratadine levels. Specifically, desloratadine had no effects on the corrected QT interval (QTc) when administered alone, at high dose, or in combination with ketoconazole or erythromycin. Preclinical studies also show that desloratadine does not interfere with HERG channels or cardiac conduction parameters even at high dose. Desloratadine is nonsedating and free of antimuscarinic/anticholinergic effects in preclinical and clinical studies. Novel antiallergic and anti-inflammatory effects have also been noted with desloratadine, a fact which may be relevant to its clinical efficacy.

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Desloratadine has recently received approval in many markets for the treatment of allergic disease. This review outlines the various facets of desloratadine's pharmacologic profile, particularly H₁-receptor binding and receptor selectivity. Desloratadine does not cause sedation and, importantly, does not interfere with cardiac conduction, a major safety consideration. Allergy is now considered to be a complex systemic immune disorder that involves many levels of cellular and chemical activation. Beyond its potent H₁-blocking effects, desloratadine also appears to inhibit important cytokine and cellular activity, suggesting an antiallergic and anti-inflammatory profile.

Pharmacodynamics

Receptor affinity studies

The potency of desloratadine's histamine H₁-receptor antagonism has been demonstrated in cellular and animal studies. Chinese hamster ovary (CHO) cells were transfected with human H₁ receptors, and the disrupted cell membranes were incubated with [³H]-pyrilamine at a concentration of 2 nM (1). Inhibition of [³H]-pyrilamine binding to H₁ receptors was assessed by Ca²⁺ flux with various antihistamines. Desloratadine had the highest affinity for H₁ recep-

tors, and the rank order of potency (K_i in parentheses) was as follows: desloratadine (0.87) > chlorpheniramine (2.0) > hydroxyzine (10) > mizolastine (22) > terfenadine (40) > cetirizine (47.2) > ebastine (51.7) > loratadine (138) > fexofenadine (175) (Fig. 1). The strong H₁ antagonism of desloratadine was confirmed in a study of cultured human bronchial smooth-muscle cells (HBSMC), which constitutively express H₁ receptors (1). Desloratadine inhibited Ca²⁺ flux in HBSMC more potently than all other compounds tested, with a rank order similar to that seen in the CHO experiment. It is important to note that significant H₁-receptor binding occurred primarily within the low to midnanomolar range, which is the concentration required for *in vivo* activity. For other antihistamines, little or no H₁-receptor antagonism was seen at nanomolar levels.

The selectivity of desloratadine for various receptor subtypes has been studied extensively (2, 3). *In vitro*, desloratadine has much less affinity for both H₂ and muscarinic receptors (15–50 times less than H₁ affinity). Moreover, desloratadine did not protect against physostigmine-induced death due to cholinergic activation in an *in vivo* mouse model. These findings have been borne out in human placebo-controlled pharmacologic and clinical studies, since desloratadine did not

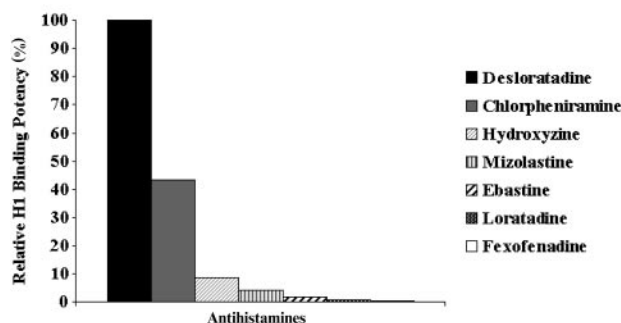


Figure 1. Relative potency of antihistamine binding to cloned human H_1 receptor in CHO cells. Adapted from ref. 1.

cause significant anticholinergic symptoms, such as dry mouth and blurred vision.

Kreutner et al. have published a series of animal studies that also reveal significant H_1 -receptor antagonism with desloratadine (2). In isolated guinea-pig ileum, desloratadine was 10 times more potent than loratadine and terfenadine in inhibiting histamine-induced contraction. In mice, desloratadine inhibited histamine-induced paw edema four times more potently than loratadine, while in guinea pigs, oral desloratadine was 2.5 times more potent than loratadine in protecting against lethal histamine injection, and the duration of this protection was longer. Desloratadine also significantly antagonized the effects of nasal and bronchial histamine challenge in guinea pigs and cynomolgus monkeys, respectively.

Antiallergic and anti-inflammatory effects

Pharmacologic treatment of allergic diseases such as seasonal allergic rhinitis or urticaria has conventionally concentrated on the blockade of mast-cell-derived histamine. Histamine is undoubtedly a major mediator in early-phase allergic responses such as sneezing, watery rhinorrhea, pruritus, and urtication. However, it is now clear that other mediators, such as mast-cell-derived tryptase (4) and cysteinyl leukotrienes (5), play an important role in vascular permeability and edema, respectively.

Allergic symptoms are caused primarily by inflammatory changes mediated by the immune system (6). The local early-phase response that follows mast-cell degranulation is linked to chronic allergic inflammation (typified by *de novo* eosinophil/basophil infiltration) by a systemic pathway. Locally produced cytokines, such as interleukin (IL)-4, IL-5, IL-6, stem cell factor (SCF), nerve growth factor (NGF), and granulocyte/macrophage colony-stimulating factor (GM-CSF), orchestrate tissue inflammation, T helper cell responses, and the maturation/release of eosinophils, basophils, and mast cells from hematopoietic precursors in the bone marrow (7–11). Simultaneously, chemoattraction of these newly formed cells or their precursors occurs

under the influence of upregulated chemokines, including eotaxin, RANTES, MIP-1 α , and IL-8 (12–15). Adhesion molecules (e.g., ICAM-1, P-selectin) aid the attachment and movement of these inflammatory cells into local allergically activated tissue (11, 16). Once *in situ*, these cells are stimulated to release additional inflammatory mediators, including preformed cytokines, enzymes, and eosinophil granule proteins, as well as newly generated cytokines and lipid mediators, which induce and maintain chronic inflammation. This concept of allergy as both local and systemic reveals many new therapeutic targets, especially in the realm of preventing chronic cellular infiltration.

Interesting preclinical studies have shown that desloratadine can inhibit many mediators, including cytokines and chemokines as well as adhesion molecules involved in systemic allergic inflammation. For instance, desloratadine downregulates histamine, tryptase, cysteinyl leukotriene (LTC₄), and prostaglandin (PGD₂) release *in vitro* from mast cells and basophils (Fig. 2) (17, 18). Lippert et al. recently reported that desloratadine reduced stimulated human mast-cell release of the inflammatory cytokines IL-3 (–32.1%), IL-6 (–32.6%), TNF- α (–64.5%) and GM-CSF (–27.8%) at nanomolar concentrations (Fig. 3) (19). Interestingly, this inhibition was superior to that of dexamethasone, ranitidine, and cetirizine. Release of the chemokine IL-8 was also inhibited by desloratadine in mast cells, basophils, and endothelial cells (20, 21), and desloratadine could also decrease release of the chemokine RANTES from nasal polyp epithelial preparations (22). Adhesion molecules such as P-selectin and ICAM-1 can be downregulated *in vitro* by desloratadine (21, 23). Finally, inhibition of *in vitro* eosinophil chemotaxis, activation, and superoxide ion generation has recently been reported (24).

These novel effects on a wide range of inflammatory mediators and associated events may enhance the ability of desloratadine to modulate the intensity of allergic responses at a systemic level, and thus reduce

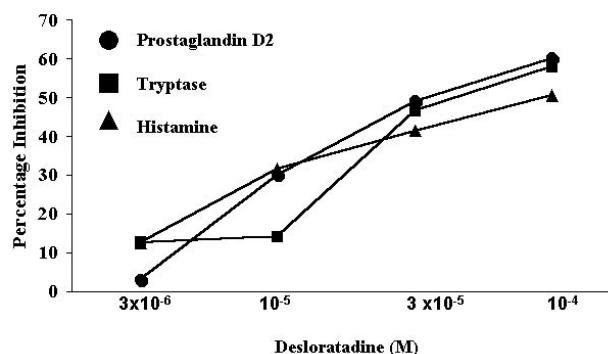


Figure 2. Effect of desloratadine on anti-Fc ϵ RI-induced release of histamine, PGD₂, and tryptase from human skin mast cells. Cells were preincubated with desloratadine for 15 min and then stimulated with anti-Fc ϵ RI for 20 min. Means of four experiments are shown. Adapted from ref. 18.

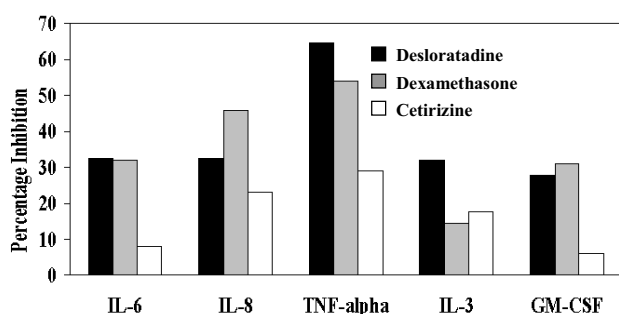


Figure 3. Effect of desloratadine, cetirizine, and dexamethasone on PMA/ionophore-induced cytokine release from human mast cells (HMC-1). Cells were preincubated with drugs for 1 h, followed by 24-h incubation with PMA/ionophore. Means of at least four experiments are shown. Adapted from ref. 19.

chronic symptoms. The *in vitro* data obtained so far are applicable not only to allergic rhinitis, but also to chronic urticaria, in which pathologic mast-cell secretion leads to increased expression of adhesion molecules and cytokines, cellular infiltration, and the formation of typical wheals with associated itch (25). The clinical impact of these *in vitro* antiallergic and anti-inflammatory effects of desloratadine will need to be confirmed in patients with allergic diseases.

Desloratadine: lack of central effects

Preclinical studies. Desloratadine is a potent H_1 -receptor antagonist without central sedating effects. Its profile has been studied extensively in various primate and nonprimate models (26, 27). High-dose desloratadine (300 mg/kg) caused no major neuromuscular changes or decreased neurologic activity, although mydriasis and ptosis were seen. In contrast, astemizole caused behavioral, autonomic, and neuromuscular depression at doses of 100–300 mg/kg. Desloratadine did not protect mice from electroconvulsion, even at high doses, thus indicating a lack of central nervous system suppression. After intraperitoneal injection of acetic acid, high doses of desloratadine (ED_{50} = 147 mg/kg) were required to suppress writhing. This is in contrast to the much lower doses of azatadine (ED_{50} = 4.8 mg/kg) required for a similar suppressive effect. Furthermore, no significant neurobehavioral effects occurred in rats at desloratadine doses of 1–12 mg/kg. Desloratadine does not penetrate the blood–brain barrier in guinea pigs after intraperitoneal injection. Neither desloratadine nor placebo inhibited the binding of radiolabeled mepyramine to brain H_1 -histamine receptors, whereas binding was reduced by nearly 50% in the presence of the sedating antihistamine, chlorpheniramine.

Human studies. In human trials of cognition and psychomotor performance, desloratadine has been

shown to be free of central sedative effects. Scharf et al. conducted placebo-controlled crossover trials with desloratadine and diphenhydramine to examine their respective effects on the Maintenance of Wakefulness Test (MWT) and the Multiple Sleep Latency Test (MSLT) (28). Diphenhydramine is known to be a sedating antihistamine and is commonly used as a comparative standard in wakefulness and cognition studies. The MWT and MSLT were the same after placebo and desloratadine. After diphenhydramine, subjects exhibited significant decrements in wakefulness in comparison to placebo and desloratadine ($P < 0.01$). Additional psychomotor profiles such as the Stanford Sleepiness Scale, the Digital Symbol Substitution Test, the Psychomotor Vigilance Test, and the Serial Add Subtract Reaction Time also revealed the equivalence of desloratadine and placebo. It is important to note that these results refer to 7.5 mg of desloratadine, which is 50% higher than the clinical dose of 5 mg.

Further confirmation of desloratadine's nonsedating character has come from a motor vehicle driving performance trial (29). In this study, subjects received 5 mg desloratadine, 50 mg diphenhydramine, or placebo in a double-blind, crossover manner. They completed a 100-km standardized highway drive in a specially instrumented car that assessed deviation in road position, speed, and brake reaction time. In all cases, desloratadine and placebo were statistically identical, while diphenhydramine significantly impaired driving skill compared with desloratadine ($P < 0.001$). Initial reports of large-scale, placebo-controlled trials of desloratadine at 5 mg once daily in seasonal allergic rhinitis have shown the incidence of sedation to be equivalent to that of placebo (30). This is consistent with the preclinical and human data outlined above.

Pharmacokinetics

In healthy individuals, desloratadine is metabolized primarily to a 3-OH form by glucuronidation. Approximately 87.1% of radiolabeled desloratadine can be recovered as metabolites from urine and feces; the proportions are 40.6% (urine) and 46.5% (feces) (data on file, Schering Corp, Kenilworth, NJ, USA). Single-dose, multiple-dose, and high-dose desloratadine studies have been performed in healthy subjects (31, 32) (see also data on file, Schering Corp., Kenilworth, NJ, USA). The pharmacokinetics of desloratadine is linear and exhibits dose proportionality. The $t_{1/2}$ of desloratadine is 21–24 h, confirming the validity of once-daily dosing. A high-dose (45 mg/day for 10 days), placebo-controlled study in healthy volunteers demonstrated a geometric mean C_{max} on day 10 of 50.1 ng/ml, while the AUC (0–24 h) was 747 ng h/ml. Despite exposure to a

high desloratadine concentration, no significant sedative or ECG side-effects were noted.

Effects of renal and hepatic failure

The effects of desloratadine on renal function have been studied specifically in the rat (26, 27). Compared with placebo, desloratadine (12 mg/kg) had no effect on total urinary volume, or potassium or sodium excretion. A single-dose desloratadine study in patients with stable renal failure of varying severity is still underway. Desloratadine does not accumulate to a dangerous extent in patients with hepatic dysfunction (data on file, Schering Corp., Kenilworth, NJ, USA). In a study of patients with mild, moderate, and severe liver disease ($n=4$ per group), the extent of exposure to desloratadine after a single 7.5-mg dose did not vary according to the severity of hepatic dysfunction. However, taken together, patients with liver dysfunction had a significantly greater C_{max} and AUC than healthy subjects, but drug exposure did not exceed that following high-dose desloratadine (45 mg/day for 10 days). No significant adverse events were noted. At the lower clinical dose of 5 mg daily, desloratadine is likely to be safe for patients with hepatic failure.

Effects of race or sex

An open-label, parallel-group study of 7.5 mg desloratadine daily was performed in male and female black and white subjects ($n=12$ per group) (33). Initially, a single dose was assessed pharmacokinetically, followed by a 14-day, multiple-dose phase. The AUC and C_{max} on day 14 were 3% and 10% higher in women than men, respectively. The AUC and C_{max} were 32% and 18% higher in blacks than whites. However, all of these differences were within the levels achieved in the 10-day, high-dose (45 mg) desloratadine study. No adverse events or clinically relevant changes accompanied these increases in drug exposure. Therefore, the 5-mg clinical dose does not require adjustment for race or sex.

Drug interactions

Toxic interactions have been reported to follow coadministration of certain nonsedating antihistamines and inhibitors of cytochrome P450 enzymes. Inhibition of hepatic cytochrome metabolism can lead to significantly increased plasma drug levels, thus increasing the risk of adverse events (34). Indeed, serious cardiac arrhythmias (torsade de pointes) and deaths have occurred due to coadministration of imidazole antifungals or macrolide antibiotics with terfenadine or astemizole (35, 36). This has led to the withdrawal of these antihistamines from most markets worldwide and has spurred intensive preapproval safety studies for all prospective H_1 -receptor antagonists. The antifungal ketoconazole and the macrolide erythromycin inhibit

cytochrome P450 3A4, and the safety of their coadministration with desloratadine (7.5 mg for 10 days) has been studied (37, 38). Compared with placebo, ketoconazole increased the C_{max} of desloratadine 1.45 times, and the AUC rose by 1.39 times. In the case of erythromycin, C_{max} and AUC for desloratadine rose by 1.2- and 1.1-fold over placebo, respectively. Levels of desloratadine remained lower than those seen after high-dose (45 mg/day for 10 days) administration, and the adverse-event profile was free of cardiac disorder (see below) and sedative effects. In conclusion, desloratadine is safe in combination with inhibitors of cytochrome P450 3A4.

Coadministration with grapefruit juice

Grapefruit juice is widely recognized to interfere with the absorption and metabolism of various drugs metabolized by cytochrome P450 3A4, including antihistamines such as terfenadine (39) and its derivative fexofenadine (40). It now appears that some of the effect of grapefruit juice can be explained by inhibition of drug metabolism by both intestinal cytochrome P450 3A4 and the P-glycoprotein pump (41). The latter system is a major excretory pathway of normal intestinal cells, but is also expressed by multidrug-resistant tumor cells. Alteration in P-glycoprotein pump function by grapefruit juice or competitive pump substrates can change the absorption and metabolism of drugs that are themselves substrates of the system. Desloratadine is not a substrate for the P-glycoprotein system (42), and coadministration with grapefruit juice did not alter C_{max} and AUC in healthy volunteers. This is in contrast to the absorption of fexofenadine, which decreased by 30% in the same volunteers. Desloratadine can therefore be administered safely with grapefruit juice.

Coadministration with food

Ingestion of medications with food can adversely affect the rate and extent of their absorption. The pharmacokinetics and bioavailability of desloratadine are statistically similar when the drug is taken in the fasting state or after a standardized meal in healthy subjects (C_{max} fasted = 3.3 ng/ml; C_{max} fed = 3.53 ng/ml, $P=0.168$) (43). Thus, desloratadine can be administered safely with meals or on an empty stomach.

Cardiac safety

As mentioned above, serious cardiac adverse events led to the withdrawal of terfenadine and astemizole from many markets. The nature of this harmful interaction is prolongation of the corrected QT interval (QTc), which can lead to the potentially fatal chaotic ventricular arrhythmia, torsade de pointes. Overdose of terfenadine and astemizole or coadministration with cytochrome

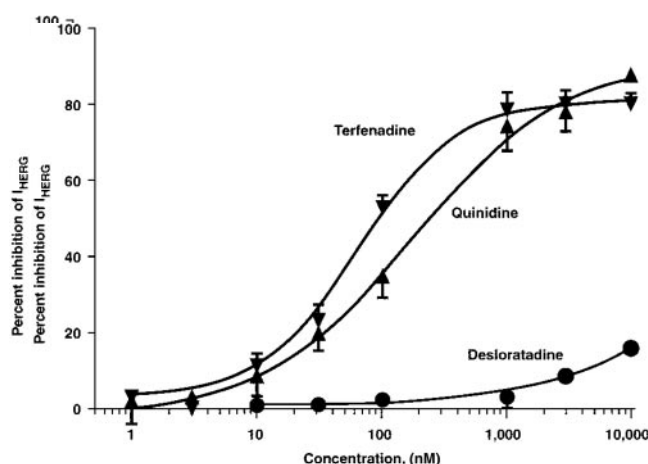


Figure 4. Lack of HERG channel inhibition by desloratadine across dose range 10–10 000 nM. Concentration-response relationship of desloratadine was demonstrated in *Xenopus laevis* oocyte HERG channels *in vitro*. Note significant inhibition of HERG channels by terfenadine and quinidine across same dose range. Adapted from ref. 27.

P450 inhibitors such as erythromycin and ketoconazole increases the risk of torsade de pointes. These drugs inhibit a delayed ventricular potassium repolarization current, IKr (44, 45). The potassium channel that controls this current is probably coded for by the human ether-a-go-go-related gene (HERG), mutations of which are a recognized cause of inherited long QT interval syndromes. The increased understanding of the molecular and pharmacologic events that lead to QTc prolongation has led to in-depth re-evaluation of all available second-generation antihistamines, and also new agents such as desloratadine.

Preclinical studies. *In vitro*, desloratadine had no effect on HERG channel function expressed in *Xenopus laevis* oocytes (27). At concentrations from 10 nM to 10 µM, desloratadine did not block HERG-related potassium currents, while terfenadine inhibited this current at a concentration of 30 nM (Fig. 4). *In vivo* studies have been performed in rats, guinea pigs, and monkeys. Heart rate rose significantly in monkeys and rats after high-dose

(12 mg/kg) desloratadine, compared with placebo. However, QTc intervals did not change in any of the animal models at desloratadine doses of 4–12 mg/kg.

Human studies. As mentioned above, the risk of QTc prolongation with terfenadine is greatly increased by overdose and coadministration with macrolide antibiotics or imidazole antifungals. Specific ECG safety studies with 7.5 mg desloratadine in combination with ketoconazole and erythromycin have been performed in healthy volunteers (37, 38). While both ketoconazole and erythromycin increased plasma levels of desloratadine, no significant effects were seen in terms of PR, QRS, QT, and QTc intervals over the 10-day course of the trial. Similarly, a high-dose study of desloratadine (45 mg/day for 10 days) demonstrated no clinically relevant changes in ECG criteria, particularly QTc (3). It should be noted that the plasma concentrations of desloratadine seen in the high-dose erythromycin and ketoconazole trials were higher than those achieved after administration of the 5-mg clinical dose. When the results of the *in vitro* work are combined with these specific ECG pharmacodynamic studies, it can be concluded that desloratadine does not cause QTc prolongation. Therefore, it carries a low risk of ventricular arrhythmia even at high plasma concentrations.

Conclusion

In summary, desloratadine has a unique profile of potent antiallergic and anti-inflammatory activity, in addition to selective, very potent H₁ blockade. The pharmacologic profile of desloratadine is safe. In particular, it is nonsedating, has no effect on cardiac conduction, and has no clinically relevant interactions in terms of coadministration with cytochrome P450 inhibitors, grapefruit juice, or food. Thus, no special cautions are required for its use in a clinical setting. This novel potent antihistamine should provide excellent clinical efficacy and safety in the treatment of patients with allergic diseases.

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