EXPERT OPINION

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Safety evaluation of desloratadine in allergic rhinitis

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Introduction: Desloratadine is a biologically active metabolite of second-generation antihistamine loratadine. It is also indicated for the treatment of allergic diseases, including allergic rhinitis.

Areas covered: A Medline search was conducted to identify preclinical and clinical studies of desloratadine. This was supplemented with additional articles obtained from online sources. The focus of this review is on the safety profile of desloratadine.

Expert opinion: The review of these data indicates that the safety profile of desloratadine is similar to other second-generation antihistamines. Desloratadine is highly selective for histamine H_1-receptors, does not cross the blood-brain barrier (BBB), and has minimal adverse events (very low sedation rate), with a better safety and tolerability than first-generation antihistamines. Desloratadine is safe and well tolerated without having central nervous system (CNS) or cardiovascular effects and with low drug interaction.

Keywords: allergic rhinitis, descarboethoxyloratadine, desloratadine, H_1-antihistamine, histamine H_1-receptor antagonist, intermittent, perennial, persistent, pharmacodynamics, pharmacokinetics, safety, seasonal, second-generation antihistamine, therapeutic use

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1. Introduction

Allergic rhinitis (AR) is a major health problem with high and ever increasing prevalence worldwide. The primary goals of treatment for AR are to reduce symptoms, which include sneezing, rhinorrhea and nasal congestion, improve quality of life and prevent the negative consequences associated with the disease [1]. Quantitatively, histamine is the most abundant mediator present during an allergic episode, thus, antihistamines constitute a first-line treatment for AR [2]. Histamine H_1-receptor antagonists have been widely used in the management of allergic disorders, such as rhinitis. In recent years, the evidence-based, clinical practice trend has been to use second-generation and more recently developed H_1-antihistamines ahead of first-generation compounds, principally because of improved safety and tolerability [1,3,4].

Treatment guidelines recommend second-generation antihistamines as first-line treatment for mild-to-moderate and intermittent allergic rhinitis [1,5]. (**Box 1**) Desloratadine was one the first H_1-antihistamines to be investigated for efficacy, safety and pharmacology following the new Allergic Rhinitis and its Impact on Asthma (ARIA) guideline classification [1,6-8]. In addition, a systematic review [6] concluded that desloratadine met the ARIA/European Academy of Allergology and Clinical Immunology (EAACI) pharmacological and clinical criteria for antihistamines.

2. Mechanism of action

Desloratadine is an orally administered, long-acting tricyclic non-sedating H_1-receptor inverse agonist also known as descarboethoxyloratadine, the primary

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Box 1. Drug summary.

Drug name (generic)	Desloratadine, descarboethoxyloratadine
Phase (for indication under discussion)	Post-marketing (Phase IV)
Indication (specific to discussion)	Allergic rhinitis
Pharmacology description/mechanism of action	H_1-receptor inverse agonist. It is a long-acting tricyclic histamine antagonist with selective H_1-receptor histamine antagonist activity. Desloratadine does not penetrate the CNS nor prolongs the QTc interval. The responsible enzyme for desloratadine metabolism has not been yet identified
Route of administration	Oral. Desloratadine can be taken with meals without food interference. Desloratadine has a low interaction with meals and other drugs, and no potentiation with alcohol intake
Chemical structure	$C_{19}H_{19}ClN_2$
Pivotal trials	[13,32-34,41,46,70,82]

active metabolite of loratadine (**Figure 1**) [2,9-14]. Histamine H_1-receptor antagonists block histamine H_1-receptor activity [15]. Desloratadine is one of the most potent antihistamines on the basis of specificity for and strength of binding affinity to human H_1-receptors [11-13,16-18]. Desloratadine dissociates very slowly from the H_1-receptor and directly inhibits multiple steps in the allergic inflammatory cascade [19], resulting in decreased capillary permeability, reduced mucus production, relaxation of the smooth muscle and reduced vasodilation, thereby reducing allergy-related symptoms (e.g., sneezing, rhinorrhea, nasal pruritus and itchy, watery eyes) [9]. Independent of its antihistaminic effects, desloratadine inhibits the expression of cell adhesion molecules, inhibits the generation and release of inflammatory mediators and cytokines and attenuates eosinophil chemotaxis, adhesion, viability and activation [14,16,17,20-22].

In vitro studies demonstrate that desloratadine, like all H_1-receptor antagonists, has anti-inflammatory properties that inhibit various mediators associated with early- and late-phase allergic responses [2,11,19,23,24], and also inhibits both the IgE- and non-IgE-mediated release of preformed histamine from human mast cells and basophils [20,25,26]. Inhibition of late-phase mediators of the allergic cascade can subsequently reduce mucinous secretions and nasal congestion [27]. Desloratadine has been shown to attenuate the release of histamine, tryptase, leukotriene (LTC_4) and prostaglandin (PGD_2) from mast cells and basophils [11,20,28]. Inhibition of interleukin-4 (IL-4) and interleukin-13 (IL-13) release by desloratadine in human basophils has also been reported [23], as it has *in vitro* stabilization of mast cells [29]. Moreover, desloratadine inhibits the activity of NF-κB with greater potency than other H_1-antihistamines [30]. In addition, desloratadine may also reduce the upper airway eosinophilic inflammation by both inhibiting the production of eosinophil chemotactic cytokines by epithelial cells and decreasing eosinophil survival and activation, either independently [21] or through potentiating the effect of topical corticosteroids [22].

Agrawal [17] demonstrated that desloratadine attenuated chemotaxis induced by platelet-activating factor, adhesion induced by TNF-α and superoxide generation. Cyr *et al.* [31] confirmed these findings *in vivo* by showing a significantly reduced eosinophil efflux into nasal mucosal tissues in patients treated with high doses of desloratadine.

3. Clinical applications

Desloratadine is approved for the treatment of seasonal allergic rhinitis and perennial allergic rhinitis [32-37], but also for intermittent and persistent allergic rhinitis [7,8]. In such studies, desloratadine has been shown to provide relief from the nasal (including nasal congestion) [36,38-43] and non-nasal symptoms of AR, providing relief after the very first dose. The administration of desloratadine once daily relieved the symptoms of rhinorrhea, nasal itching, sneezing and postnasal drip drainage significantly in patients with perennial allergic rhinitis [36,44]. Desloratadine had an overall beneficial effect on the symptoms of AR, with an improvement over placebo > 30% [8,34,36,41,42,45-47].

Desloratadine has demonstrated beneficial effects in relieving symptoms affecting both the upper and lower airways [48]. In a double-blind, placebo-controlled trial in 331 patients with mild asthma having seasonal allergic rhinitis and nasal congestion, desloratadine 5 mg once daily for 4 weeks induced improvements in seasonal allergic rhinitis and asthma symptom scores, with a decrease of inhaled bronchodilator used as rescue medication [41]. Studies have shown similar efficacies in perennial AR and asthma for desloratadine and various second-generation antihistamines [37,49,50]. However, it should be noted that desloratadine has no indication for the relief of asthma symptoms.

Many studies comparing the efficacy of second-generation antihistamines have found no clinically relevant differences among them [35,37,38,51,52].

4. Safety evaluation

Desloratadine has a long half-life (27 h) which allows its once-daily administration [53,54]. Desloratadine is rapidly absorbed, with a time to maximum concentration of ~ 3 h after oral administration [55]. Desloratadine has linear pharmacokinetics

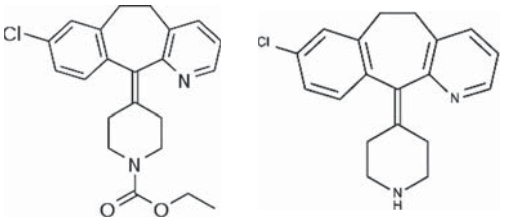

Figure 1. Tridimensional structure of desloratadine. The chemical name is 8-chloro-6,11-dihydro-11-(4-piperdinylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, an empirical formula of $C_{19}H_{19}ClN_2$, and a molecular weight of 310.8.

over the 5 – 20 mg dose range [56]. Approximately 87% of the parent drug is equally distributed between urine and feces as metabolite [10].

4.1 Sedation and CNS impairment

Second-generation antihistamines are more lipophobic than their predecessors, possessing a different ionic charge. In addition, they are made up of larger molecules than the first-generation agents. These three factors when combined appear to be what makes it substantially more difficult for these molecules to cross the blood-brain barrier (BBB) [57]. Numerous studies have found desloratadine to be relatively free of sedative side effects or effects on performance, even at excessive doses. This is most likely due to its apparent lack of penetration of the BBB [6,34-36,41,47,58-62]. In controlled clinical trials, at the recommended dose of 5 mg daily, desloratadine induced little incidence of somnolence as compared to placebo, no effect on psychomotor performance [63], no impairment of driving performance [64] and no impact on standard measures of flight performance, which included exacerbation of subjective sleepiness or tasks related to flying [54,65].

There was no difference between the effects of desloratadine and placebo groups when administered alone or with alcohol in terms of cognition testing, alertness and self-rated somnolence [6].

4.2 Cardiovascular effects

Some second-generation antihistamines, most notably terfenadine and astemizole, have been associated with prolongation of the QT interval and the development of *'torsades de pointes',* a potentially fatal ventricular arrhythmia [66]. This rare adverse event has been associated with greatly elevated blood levels of these drugs, resulting from overdose, hepatic dysfunction or interactions with other drugs that inhibit their metabolism [67]. The cardiovascular effects of desloratadine have been extensively studied both in adults and in children [56,68-70]. In these studies, no patient treated with desloratadine experienced a cardiovascular adverse event. Treatment with desloratadine revealed no clinically relevant changes in mean ventricular rate or PR, QRS, QT or QTc intervals when compared with placebo [11,62,68,71]. Even with high single doses of 45 mg daily for 10 days, no clinically relevant adverse events (AEs) were reported [10].

Overall, the adverse cardiovascular effects of antihistamines appear not to be a hallmark of all second-generation agents [72], since loratadine, cetirizine, azelastine, fexofenadine, bilastine and rupatadine are not associated with *'torsades de pointes'* or other ventricular arrhythmias [67,73-75].

4.3 Anticholinergic effects

Both *in vitro* and animal *in vivo* studies suggest that desloratadine has no relevant effects on muscarinic receptors [12,18]. The incidence of dry mouth for desloratadine was 3% compared with 2% of placebo [54].

4.4 Safety in clinical studies

Results of studies conducted during clinical development show that desloratadine exhibited an AE profile similar to placebo [32,33,36,39,41,42,44,46,48,50,76]. Most AEs were of mild to moderate severity and occurred with similar frequency among patients treated with desloratadine and placebo. The most commonly reported AEs included headache, dry mouth, pharyngitis, upper respiratory tract infection, coughing, somnolence and gastrointestinal events. Study discontinuations related to AEs were minimal (5% in patients receiving desloratadine compared with 3% in placebo) [44]. In clinical trials [10,54] undesirable effects with desloratadine were reported in 3% of patients over those treated with placebo. The most frequent of AEs reported over placebo were fatigue (1.2%), dry mouth (0.8%) and headache (0.6%). The most common AEs leading to early discontinuation were related to viral upper respiratory tract infections [36].

In multiple-dose placebo-controlled trials [10], 2,834 patients aged 12 years or older received doses from 2.5 – 20 mg of desloratadine daily, with 1,655 of them receiving the recommended daily dose of 5 mg. Under these trials desloratadine showed a similar AE rate to placebo. The percent of patients who withdrew prematurely due to AEs was 2.4% for desloratadine compared with 2.6% for placebo.

All AEs that were reported in ≥ 2% of patients and were more common than those for the placebo group are listed in **Table 1** [10]. No serious or unexpected AEs were attributed to desloratadine. No clinically relevant changes in mean vital signs, clinical laboratory test results or electrocardiograms, including QTc intervals, were observed compared with baseline values or between compared with placebo [36,44].

Similar results were found in pediatric studies [69,77-80]. No statistical significant difference was noted in treatment-related AEs when comparing desloratadine with placebo. The most common AEs were irritability, diarrhea, somnolence and insomnia [77].

Preclinical and clinical studies have demonstrated that desloratadine, like other second-generation antihistamines, is not associated with cardiovascular toxicity while somnolence,

Table 1. Adult and adolescent patients with allergic rhinitis treated with desloratadine (incidence of adverse effects reported by ≥ 2% of patients) [10].

Adverse event	Placebo (n = 1,652)	Desloratadine 5 mg (n = 1,655)
Pharingitis	2.0%	4.1%
Somnolence	1.8%	2.1%
Dry mouth	1.9%	3.0%
Myalgia	1.8%	2.1%
Dysmenorrhea	1.6%	2.1%
Fatigue	1.2%	2.1%

commonly associated with older antihistamines, occurred at similar rates in placebo and desloratadine treated patients.

No clinical data relating to desloratadine reveal any particular hazards for humans based on conventional studies of pharmacological safety repeated dose toxicity, genotoxicity and toxicity to reproduction. The lack of carcinogenic potential was demonstrated in studies conducted with both desloratadine and loratadine [10,54].

4.5 Post-marketing data

The following spontaneous AEs have been reported during the marketing of desloratadine: tachycardia, palpitations, rare cases of hypersensitivity reactions, psychomotor hyperactivity, seizures, elevated liver enzymes including bilirubin and very rarely hepatitis [10].

Amongst four post-marketing surveillance studies in 77,880 subjects (42,775 with seasonal allergic rhinitis) [71], AEs were reported by 287 subjects (0.37%). The most commonly reported AE related to treatment were fatigue (0.07%), headache (0.07%), dry mouth (0.04%) and nausea (0.03%). Most of these AEs were of mild to moderate severity. Overall in the four studies, 166 subjects (0.21%) discontinued treatment because of an AE. Headache (0.05%), fatigue (0.04%), nausea (0.03%) and dry mouth (0.01%) were the most frequently reported AEs causing cessation of treatment. Tolerability was rated as excellent/good by 99.1% of researchers and 98.5% of subjects. In a post-marketing surveillance study in England with 8,001 AR patients, desloratadine also showed good tolerability [81].

Recently, the Aerius Control Clinical and Evaluative Profile of Treatment (ACCEPT) program developed two studies, one for intermittent (ACCEPT-1) [46] and one for persistent AR (ACCEPT-2) [82], to assess the efficacy and safety of desloratadine for AR patients using the ARIA classification. The ACCEPT studies [46,82] reported that desloratadine was effective and safe for both intermittent and persistent AR. In both these placebo-controlled, multicenter, randomized clinical trials, the incidences of AEs related to treatment (headache, fatigue, sedation, pruritus, nausea and thirst) were low and similar between desloratadine (7.2 – 10%) and placebo (7.0 – 8.4%). The rate of treatment-related AEs was similar between both groups, confirming the results of previous studies that found desloratadine to be a safe and effective drug [32,33,36,39,41,42,44,46,50,76].

4.6 Safety in special populations

Desloratadine can be confidently administered once daily in patients with AR regardless of age, sex or ethnicity [55,83], and in both adult and pediatric patients [10,54].

4.6.1 Patients with renal impairment

Plasma concentrations were shown to be increased compared with patients with normal renal function. In patients with severe renal impairment or on hemodialysis, Cmax and AUC values increased by approximately 1.7 and 2.5 folds respectively, with desloratadine and 3-hydroxydesloratadine being poorly removed by hemodialysis. Plasma protein binding of desloratadine and 3-hydroxydesloratadine was unaltered by renal impairment [10,11]. Dosage adjustment for patients with renal impairment is recommended [10], with a starting dosage of 5 mg every other day [54].

4.6.2 Patients with hepatic impairment

Regardless of their severity, those patients had approximately a 2.4 fold increase in AUC compared with healthy subjects [10]. An increase in the mean elimination half-life of desloratadine was observed in patients with hepatic impairment. Dosage adjustment for patients with hepatic impairment is recommended [10], with a starting dosage of 5 mg every other day [54].

Alcohol can impair performance, especially when administered with antihistamines causing sedation. Desloratadine does not, however, potentiate alcohol-induced performance impairment, even at higher doses than those recommended [2].

A subset of the general population (6%) and of the African-American population (20%) are considered to be poor desloratadine metabolizers because of a decreased ability to form the metabolite 3-hydroxydesloratadine [84], with this being defined as having a 3-hydroxydesloratadine to desloratadine exposure ratio of < 10% or a desloratadine half-life of ≥ 50 h. However, despite increased exposure to desloratadine in poor metabolizers, AE profiles were similar to placebo-treated patients with no difference in the cardiovascular safety profile [10,84].

4.6.3 Pregnancy (category C) and lactation

Desloratadine was not teratogenic in animal studies (rats and rabbits) but is not currently recommended for use in pregnant or breast-feeding women [54]. Studies of the parent molecule, loratadine, in female patients during the first trimester of pregnancy have shown no adverse outcomes compared with matched control cohorts [85].

4.6.4 Drug interactions

Clinical studies have examined the co-administration of desloratadine with several known inhibitors of the CYP system, with ketoconazole [68,86], azithromycin [87], erythromycin [88], cimetidine [10,86] or fluoxetine [89]. These studies

confirmed that co-administration does not induce clinically relevant alterations in ECG or pharmacokinetic parameters. Desloratadine demonstrated little or no inhibition for inhibitors of certain human liver cytochrome P-450 enzymes (CYP1A2, CYP3A4, CYP2C19, CYP2C9 or CYP2D6) [90].

In addition, desloratadine is devoid of drug-food interactions. Under fed and fasted conditions, the plasma concentration-time profile of desloratadine was similar, and the relative bioavailability of desloratadine was also comparable, indicating that desloratadine may be administered with or without meals [91]. In addition, administration with grapefruit juice, a known inhibitor of CYP3A4 and OATP, did not alter the absorption or bioavailability of desloratadine [92].

4.7 Comparison with safety of other drugs

4.7.1 With first-generation antihistamines

Desloratadine shows less potential for sedation than the first-generation antihistamines (e.g., chlorpheniramine, diphenhydramine) owing to their comparative inability to penetrate the BBB [93] and occupy H_1-receptors in the CNS [15,57,60,94]. Conversely, earlier antihistamines significantly impaired performance and learning capability, leading to impairment of driving performance, significant decreases in alertness and cognitive function [58] and increased daytime somnolence compared with placebo and desloratadine [13,57,64,65].

4.7.2 With other second-generation antihistamines

Second-generation H_1-antihistamines are relatively free from CNS, antimuscarinic, antiserotonin and anti-α adrenergic adverse effects [3,95]. Although, the rates of drowsiness and sedation for second-generation antihistamines are low [52], several studies report that levocetirizine and cetirizine carried a greater risk of sedation than desloratadine [93,96,97]. The second-generation H_1-antihistamines do not exacerbate the CNS effects of co-administration with alcohol or other CNS-active substances [52].

The early non-sedating antihistamines (terfenadine and astemizole) were withdrawn because of cardiac toxicity, particularly tachycardia and corrected QT interval prolongation leading to *'torsades de pointes'* [2,66,67]. Second-generation antihistamines, including desloratadine, loratadine, cetirizine, fexofenadine, rupatadine and bilastine are not associated with significant QTc interval prolongation [68,72-75], even when administered at several times the recommended dose, or concomitantly with agents that inhibit their metabolism and elimination [67]. Rather, the cardiotoxic effects of some of these antihistamines appear to be related to their potassium channel-blocking affinity. By virtue of their weak binding to this channel, loratadine (and its metabolite, desloratadine), cetirizine and fexofenadine, have been identified as the antihistamines with the least cardiotoxic potential [72]. The data indicate that the potential to cause ventricular arrhythmias is not a class effect of second-generation antihistamines [67,72].

All second-generation antihistamines are well tolerated, with few AEs having been identified in the available studies in adults and children [51,78]. However, differences among the antihistamines in relation to a lack of significant interaction with drug transporter molecules and somnolence over placebo may provide some advantages for the overall profile of desloratadine compared with fexofenadine and levocetirizine [59,87,98].

The safety profiles of bilastine 20 mg, rupatadine 10 mg and desloratadine 5 mg, once daily, were comparable to placebo, with headache, somnolence and fatigue being the three most common AEs reported by $\geq 2\%$ of patients [73-75,99].

Radioligand-receptor binding studies for the human histamine H_1-receptor have demonstrated that desloratadine is 15 – 20 fold more potent than loratadine and terfenadine, and has 50 – 194 fold greater affinity than cetirizine, loratadine and fexofenadine [12]. Desloratadine undergoes less extensive first-pass metabolism than loratadine, and has a mean elimination half-life of 27 h compared with 12 – 15 h for loratadine [2,10].

5. Conclusions

Desloratadine is a potent, once-daily, orally active, non-sedating, non-impairing, selective histamine H_1-receptor antagonist. It also inhibits multiple steps in the allergic inflammatory cascade. Desloratadine has demonstrated efficacy in relieving symptoms of AR, including nasal congestion, which is considered the most bothersome symptom of allergic rhinitis. Numerous clinical studies have demonstrated that desloratadine is safe, well tolerated and free of serious cardiac effects. Desloratadine has not been associated with sedation or cognitive and psychomotor impairment. Pharmacokinetic studies have demonstrated a low propensity for drug-drug or drug-food interactions, with no indications that it potentiates the effects of alcohol. Dose reductions are required for patients with renal or hepatic impairment.

6. Expert opinion

Desloratadine is a biologically active metabolite of second-generation antihistamine loratadine which is indicated for the treatment of allergic diseases, including allergic rhinitis. Desloratadine has a broad indication in allergic rhinitis as recommended in international guidelines being considered as a first-line therapy for the treatment of allergic rhinitis in all its levels of severity. It has indication for seasonal and perennial allergic rhinitis and has been the first drug among second-generation antihistamines to obtain indication for both intermittent and persistent allergic rhinitis, following the new ARIA classification. In addition to its efficacy in nasal and ocular symptoms and in the quality of life of patients with allergic rhinitis, desloratadine has an excellent safety profile which represents, like happens with other second-generation H_1-blockers, better safety and tolerability than first-generation antihistamines. Desloratadine is highly selective for histamine H_1-receptors, does not cross the BBB, and has

minimal adverse events, particularly having a very low sedation rate and drug interaction as well as no CNS or cardiovascular effects.

Under our opinion, physicians prescribe and will likely keep prescribing it based on the once daily administration and minimal induction of sedation. However, since there are no clinical data on its potential effectiveness in topical nasal administration, either in monotherapy or in association with other drugs such as intranasal corticosteroids, some investigations will be needed in this direction in the near future. In 5 years time desloratadine will likely remain as an excellent antihistaminic drug, especially because of its high safety profile.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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