Desloratadine: a review of pharmacology and clinical efficacy in allergic rhinitis and urticaria

Desloratadine is a second-generation nonsedating antihistamine currently used in the treatment of allergic rhinitis and chronic idiopathic urticaria. It is the major active metabolite of loratadine. The binding affinity of desloratadine for H1 receptors is the highest among all antihistamines. Besides the effects of desloratadine on H1 receptors, it may also reduce the release of anti-inflammatory cytokines and other mediators involved in the early- and late-phase allergic response. Desloratadine is well-tolerated, and most adverse events reported are mild/moderate and experienced by a small proportion of the patients. Many large, randomized, double-blind, placebo-controlled trials have confirmed that desloratadine is effective against symptoms of intermittent and persistent allergic rhinitis. Patients with chronic idiopathic urticaria also experience marked relief of symptoms upon treatment with desloratadine, since urticarial symptoms in chronic idiopathic urticaria are largely mediated by histamine.

KEYWORDS: allergic rhinitis, allergy, chronic idiopathic urticaria, desloratadine, histamine, inflammation

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Over 80 million people in Europe are affected by some form of allergic disease, according to the Global Allergy and Asthma European Network estimates. Among these diseases, the prevalence of allergic rhinitis (AR) is increasing, and is estimated to be up to 39% in children and 40% in adults. A total of 70% of the cases occur before the age of 30 years. In addition to clinical symptoms including sneezing, nasal pruritis and rhinorrhea, AR significantly reduces quality of life, and negatively impacts school and work performance. Each year, millions of people experience complications such as sinus disease and otitis media associated with AR. Furthermore, direct and indirect costs, including prescription treatments and lost productivity attributable to AR, exceed US$5.6 billion in the USA and €3 billion in Europe [1]. It has been estimated that up to 3.8 million school or work days are lost per year in the USA due to AR. The interrelation between rhinitis and asthma has been demonstrated in various studies [2–4]. In one study, 34% of children with perennial AR and 13% of those with seasonal AR developed asthma after a follow-up period of 8–11 years [3]. Conversely, almost 57.7% of children with asthma had required medications for rhinitis within the last year, and 68.8% had findings consistent with AR in another study [4]. Consequently, two main guidelines considering the diagnosis and treatment of AR have recently been produced: Allergic Rhinitis and its Impact on Asthma (ARIA) [5], and the European Position Paper on Nasal Polyps and Rhinosinusitis (EP^3OS) [6]. Chronic idiopathic urticaria (CIU) is also a frustrating condition for patients, and has a negative impact on the quality of life of affected patients and limits daily activities. Characterized by hives and pruritus, CIU may result in sleep disturbances and social restrictions. The true incidence of CIU is unknown; however, it is believed to occur in 0.1–3% of the population. Antihistamines are the mainstay of therapy for CIU [7].

Histamine has a major role in the pathogenesis of allergic rhinitis and urticaria via the histamine H1 receptors. Nonsedating antihistamines are the principal first-line therapy for AR and CIU according to the European Academy of Allergology and Clinical Immunology (EAACI) and ARIA guidelines [5,8]. Many antihistamines are currently available, which have shown effectiveness in the treatment of related symptoms. First-generation antihistamines, such as chlorphenyramine and diphenhydramine, are not recommended by any of the major therapeutic guidelines because they are highly lipophilic, substantially pass the blood–brain barrier and result in sedation, impaired cognitive functions, sleep disturbances and reduced quality of life. Newer antihistamines are associated with a better safety profile, lower incidence of sedation and cardiovascular adverse effects, as well as higher potency, faster onset and longer duration of action.

Desloratadine is a second-generation nonsedating antihistamine used currently in the treatment of AR and CIU. This review focuses

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on desloratadine, with specific emphasis on its mechanism of action, clinical efficacy and safety in the treatment of patients with AR and CIU.

Introduction to desloratadine

Desloratadine is an orally administered nonsedating antihistamine that first became available in 2001 for the treatment of AR. Desloratadine (also referred to as descarboethoxyloratadine) is a tricyclic histamine antagonist with the chemical name 8-chloro-6,11-dihydro-11-(4-piperdinylidene)-5H-benzol[5,6]cyclohepta[1,2-b]pyridine. The empirical formula of desloratadine is $C_{19}H_{19}ClN_2$ and the molecular weight is 310.8 Da. Desloratadine selectively inhibits peripheral histamine H1 receptors and has been suggested to have anti-inflammatory actions as well. Desloratadine is currently approved for the treatment of CIU and AR, including seasonal, perennial, intermittent and persistent AR. Desloratadine is well tolerated and has a favorable side-effect profile with a low frequency of CNS and cardiovascular effects, and negligible drug interaction potential (TABLE 1) [9].

Chemistry

Desloratadine is the major active metabolite of loratadine [9]. Its chemical structure is illustrated in FIGURE 1. Although availability changes in distinct regions of the world, desloratadine has four commercially available formulations: the tablet form containing desloratadine 5 mg; the syrup form containing desloratadine 0.5 mg/ml; the orally disintegrating tablet containing desloratadine 2.5 mg or 5 mg; and extended-release tablets containing desloratadine 2.5 mg plus pseudoephedrine sulfate 120 mg, and desloratadine 5 mg plus pseudoephedrine sulfate 240 mg.

Pharmacodynamics

In vitro studies

Desloratadine displays greater affinity for H1 receptors than H2 receptors [10]. The binding affinity of desloratadine for H1 receptors is highest among all antihistamines, for example, 15–20 times higher than loratadine and terfenadine, and 200 times higher than fexofenadine. Studies in isolated guinea pig ileum demonstrated that desloratadine was more potent than loratadine and terfenadine in antagonizing histamine-induced contractions. Similar findings were also found in human cell lines [10–12]. Once bound to the H1 receptor, dissociation is very slow (pseudoirreversible antagonism), yielding prolonged clinical activity that permits once-daily dosing [11].

The affinity of desloratadine for peripheral muscarinic receptors was also lower than that of H1 receptors. Antimuscarinic side effects such as dry mouth, dry eyes, urinary retention and blurred vision were not observed at standard therapeutic doses [13]. Desloratadine is unlikely to exert central antimuscarinic effects at therapeutic dosages (5 mg recommended dose) in normal adults. Several studies in healthy volunteers and patients with allergic rhinitis have demonstrated that desloratadine has no sedative or performance-impairing activity compared with placebo [14,15].

On the other hand, it has been suggested that desloratadine may competitively inhibit muscarinic receptors of the heart and may interfere with normal cardiovascular function, resulting in tachycardia [13,16]. In an *in vivo* study in rats, high-dose desloratadine (1 mg/kg) caused significant blockade of cardiac M2, and possibly cardiac M3 receptors. This was demonstrated by significant inhibition of oxotremorine-mediated positive and negative inotropic events and bradycardia by desloratadine [13]. However, these effects were observed at doses greater than those recommended for antihistaminergic therapy. Desloratadine did not induce changes in QTc interval or other clinically relevant electrocardiogram (ECG) changes in healthy subjects, and when administered either alone in a higher dose or in combination with ketoconazole or erythromycin [12,17]. No clinically significant cardiac adverse events were seen in clinical trials of desloratadine. The incidence of cardiac adverse events was even the same in poor metabolizers of desloratadine, in whom very high serum concentrations are achieved [18].

In vivo studies in experimental animals

Desloratadine administered orally inhibited histamine-induced paw edema in mice in a dose-dependent manner. Desloratadine also reduced acute bronchospasm in allergic monkeys exposed to antigen challenge. In guinea pigs exposed to lethal doses of histamine, desloratadine provided greater protection than loratadine [10]. Handley *et al.* reported that oral desloratadine was more potent than loratadine in inhibiting wheal-and-flare in the guinea pig [19].

Anti-inflammatory activity

Besides effects of desloratadine on H1 receptors, it may also reduce the release of anti-inflammatory cytokines and other mediators involved in early- and late-phase allergic

response. Desloratadine has been shown to inhibit the release of preformed histamine from human mast cells and basophils following allergen challenge [20]. Desloratadine inhibits both histamine-dependent and -independent human umbilical vein endothelial cell activation, and expression of cell-adhesion molecules including intracellular adhesion molecule-1 (ICAM-1) in human nasal epithelium, which play an important role in the accumulation of inflammatory cells in tissues [9,21]. Desloratadine inhibits histamine, tryptase, leukotriene C_4 (LTC_4) and prostaglandin D_2 (PGD_2) release from various human cells [20,22,23]. It also inhibits interleukin (IL)4 and IL13 secretion from human basophils [24]. This inhibition was thought to be secondary to reduced nuclear factor-κB (NF-κB) activity by desloratadine. Desloratadine was found to inhibit eosinophil chemotaxis, adhesion to endothelial cells and generation of superoxide radicals *in vitro* in a dose-dependent manner using eosinophils obtained from patients with asthma or allergic rhinitis [25], and to induce eosinophil apoptosis [26]. Inhibition of NF-κB activity may also be responsible from the observed anti-inflammatory effects of desloratadine [27]. All these studies on the anti-inflammatory effects of desloratadine are *in vitro* studies with concentrations of desloratadine much higher than the relevant clinical concentrations. Murine studies have also shown that antihistamines inhibit bronchial inflammation and hyperresponsiveness by depressing cytokine production by T cells [28,29]. Experimental studies in patients with seasonal AR suggest that these anti-inflammatory properties of desloratadine may have clinical relevance [30,31]. In one study in patients with AR and asthma, desloratadine treatment reduced the circulating number of eosinophils [30]. The anti-inflammatory results obtained with relevant clinical concentrations are likely due to the inverse agonist activity of desloratadine on the H1 receptor, but an independent mechanism from the H1 receptor is also considered by some investigators [32,33].

Pharmacokinetics

Desloratadine is rapidly absorbed after oral administration. Conventional tablets and oral solution are bioequivalent. Peak plasma concentrations occur 3 h following administration of the tablet formulation, and 6–7 h following fixed combination extended-release preparation [34]. Antihistaminic effects arise within 1 h of administration. The pharmacokinetic profile is linear across the single dose range of 5–20 mg, C_{max} and AUC values increase in a dose-proportional manner [35]. Steady-state plasma concentrations were reached by day 7 during administration of 5 mg daily in healthy adult volunteers [34]. The mean steady state plasma C_{max} and AUC after dosing were 4 and 56.9 ng/ml, respectively [34]. Grapefruit juice (an inhibitor of drug transport systems such as organic anion transport polypeptide and P-glycoprotein) did not alter the bioavailability of desloratadine, but reduced the rate and extent of absorption of fexofenadine [36]. Food intake does not alter bioavailability either – C_{max} and AUC values were found to be similar after a high-fat, high-calorie meal or following overnight fasting [37]. Plasma protein binding is 82–87% for desloratadine, and 85–89% for 3-hydroxydesloratadine [9]. The elimination half-life of desloratadine is 27 h; therefore, once-daily dosing is appropriate [34].

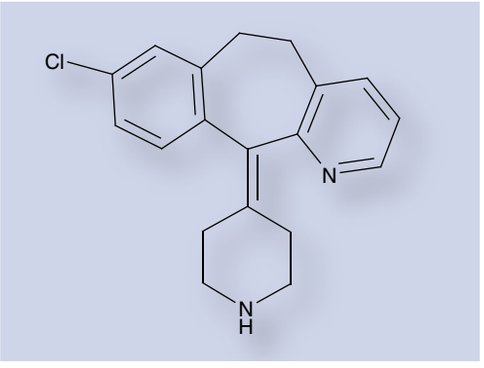

Figure 1. Desloratadine.

Desloratadine is metabolized to 3-hydroxydesloratadine, an active metabolite that subsequently undergoes glucuronidation. Other active metabolites are 5-OH, 6-OH and dihydroxydesloratadine. A total of 6–7% of the general population are poor metabolizers. The frequency of poor metabolizers is higher in Blacks than Caucasians or Hispanics. Safety of the drug is similar between the groups; therefore, no dose adjustment is indicated [34,38]. Approximately 87% of a radiolabeled oral dose of desloratadine is excreted in urine and in feces in equal proportions as metabolic products [14,17].

Systemic exposure to desloratadine after administration of 1 mg for children aged between 6 months and 1 year, 1.25 mg in children 1–5 years old or 2.5 mg in 6–11 year-olds in an oral syrup formulation was similar to that observed in previous studies of adults receiving 5 mg desloratadine [39,40]. Elderly patients had prolonged $t_{1/2}$ periods and higher plasma desloratadine concentrations than younger individuals, but this was not considered clinically relevant. The pharmacokinetic

profile was found to be similar in men versus women, and in Blacks versus Caucasians [40]. In patients with hepatic or renal impairment, AUC and elimination half-life are increased and clearance is decreased; therefore, dosage adjustments are recommended in patients with any degree of hepatic or renal impairment [41,101]. Desloratadine is poorly removed by hemodialysis. The recommended dose for patients with hepatic or renal dysfunction is 5 mg every other day (US label) [101]. Clarinex® Reditabs® contain aspartame, which is subsequently metabolized to phenylalanine in the GI tract; therefore, patients with phenylketonuria should be warned [101].

Drug interactions

Desloratadine has a favorable drug interaction profile compared with other antihistamines. Desloratadine minimally inhibits CYP isoenzymes 1A2, 2C9, 2C19, 2D6 and 3A4 at much higher plasma concentrations than therapeutic levels; therefore, interaction is minimal with drugs metabolized by this system. Desloratadine causes no clinically relevant pharmacodynamic or electrocardiographic interactions when coadministered with inhibitors of major CYP isoenzymes, including erythromycin, ketoconazole, cimetidine and fluoxetine. Antacids did not alter the absorption of desloratadine [25].

Clinical efficacy

The classification of AR was amended in 2008, and the ARIA classification divides AR into 'intermittent' and 'persistent' AR, while the former classification uses the terms 'seasonal' and 'perennial' AR. Thus, the studies performed before ARIA classification was established designate patients as having 'seasonal' and 'perennial' AR, and more recent studies use the ARIA classification. For the purpose of easy reading and comparison, seasonal and intermittent AR studies and perennial and persistent AR studies will be reviewed together, while it is not correct to use these terms interchangeably. Only randomized placebo-controlled studies or randomized comparative studies of desloratadine in AR and urticaria and published in English were reviewed.

Efficacy of desloratadine in patients with seasonal or intermittent allergic rhinitis

The efficacy of desloratadine was evaluated in subjects with a greater than 2-year history of seasonal or intermittent AR in a number of randomized, double blind, placebo-controlled studies where symptom scores, rhinitis quality of life questionnaire (RQLQ) and peak nasal inspiratory flow (PNIF) were used as efficacy parameters. These studies demonstrate that desloratadine was more effective than placebo in patients with seasonal/intermittent AR as classified by the ARIA workshop group.

In the first study, Nayak and Schenkel treated 346 subjects with intermittent AR with desloratadine 5 mg/day, and found that desloratadine treatment reduced mean morning/evening nasal congestion scores as well as total symptom scores (TSS) during the study period, started as early as day 2 compared with placebo [42]. In the second study, Bhatia *et al.* randomized 61 subjects with seasonal AR and tree or grass pollen allergy either to receive desloratadine or budesonide nasal spray (32 µg/day). PNIF, which is a measure of nasal airflow/patency, was evaluated in both groups. Although budesonide treatment was associated with a greater increase in evening PNIF and total PNIF rate compared with desloratadine, both budesonide and desloratadine groups had similar improvement from baseline in scores for individual symptoms, total AR symptom scores and quality of life scores [43].

A third study reported by Meltzer *et al.* established the efficacy of desloratadine in 220 subjects with a 2-year history of mild-to-moderate seasonal AR. At the end of the study, desloratadine 5 mg/day significantly improved total nasal symptom scores (TNSS) and total symptom scores compared with placebo ($p = 0.02$, $p = 0.03$, respectively) [44]. In a recent study of Pradalier *et al.*, 483 patients with seasonal AR of more than 2-year duration were randomly assigned to receive desloratadine 5 mg or placebo for 14 days. TSS and TNSS reduced significantly after desloratadine therapy. Desloratadine was also associated with a significant reduction in RQLQ scores [45].

In a 4-week, multicenter, double-blind, placebo-controlled study of Berger *et al.*, 331 patients with seasonal AR were given desloratadine or placebo. Significant reductions with desloratadine were noted in morning/evening reflective TSS, TNSS and total non-nasal symptom scores (TNNSS) throughout the study period. Desloratadine also improved nasal congestion and asthma symptoms that started on day 15, compared with placebo. These effects were maintained throughout the study period [46]. Two other randomized placebo-controlled studies of desloratadine also revealed similar results with improvement in symptom scores [47] and nasal airflow [48].

Comparative studies of desloratadine with other antihistamines in seasonal AR have been performed. In one study, diphenhydramine was

found to be superior to desloratadine in symptom control among patients with moderate-to-severe seasonal AR. Somnolence occurred more frequently with diphenhydramine (22.1%) compared with desloratadine (4.5%) [49]. Levocetirizine more effectively improved nasal symptoms and airflow and reduced leukocyte infiltration and cytokine levels when compared with desloratadine in two studies in patients with seasonal AR [50,51]. The montelukast–cetirizine combination was more effective than montelukast–desloratadine in terms of nasal symptoms, inflammatory cells and cytokine levels in seasonal AR patients [52]. On the other hand, fexofenadine and desloratadine were found to be equally effective in improving nasal peak flow and nasal symptoms in seasonal AR [53,54]. Desloratadine also improved asthma symptoms and forced expiratory volume in 1 s (FEV_1) in patients with seasonal AR and symptoms of asthma. Improvements in asthma symptoms were comparable for both active treatment groups [55]. Desloratadine and montelukast showed similar attenuation of the response to nasal mannitol challenge in patients with AR [56].

The current strategy in allergy treatment advocates continuous treatment throughout the entire period of allergic exposure, rather than symptomatic treatment. Consequently, in all the above-mentioned trials, desloratadine was used in a continuous fashion. We have also evaluated the clinical efficacy and the anti-inflammatory activity of regularly administered desloratadine versus on-demand use in children with AR due to pollen allergy. The patients in the on-demand group were advised to take desloratadine 5 mg daily when the symptoms started, and stop when recovered. There was no difference between regular and on-demand groups considering the symptom scores, inflammatory markers including eosinophil cationic protein levels in nasal lavage, peripheral eosinophil counts, serum total IgE levels and nasal flow rates measured with rhinomanometry. Our study demonstrated that on-demand use of desloratadine during the pollen season was clinically as effective as regular treatment. The clinical implication of this suppression remains to be determined [57].

Efficacy of desloratadine in patients with perennial or persistent allergic rhinitis

Many large, randomized double-blind, placebo-controlled trials have confirmed that desloratadine is effective against symptoms of perennial or persistent AR. In a 4-week, multicenter study of Kim *et al.*, 1179 subjects with perennial AR of greater than 2-years duration were randomly assigned to receive desloratadine 5 mg or placebo for 4 weeks. Severity of symptom scores during a 30-day screening period was recorded by the subjects. The primary efficacy end point was the mean change in reflective TSS from baseline during the study period, which was significantly better with desloratadine. Secondary efficacy end points were TNSS and TNNSS, which were improved with desloratadine compared with placebo. There were also greater improvements in the morning PNIF rates in the desloratadine group when compared with the placebo group. Adverse event rates were similar between the two groups, the most frequent being headache (6% in both groups) [58]. Simons *et al.* similarly conducted a randomized, double-blind, placebo-controlled, parallel group trial involving 676 subjects with moderate perennial AR [59]. Desloratadine was found to be effective against symptoms of perennial AR. This effect started as early as day 2, and was maintained until the end of 4 weeks' period. Desloratadine improved the morning/evening instantaneous TSS ($p = 0.005$) and morning/evening reflective TNNSS ($p = 0.023$) better than placebo, and also improved individual instantaneous nasal symptom scores [59]. Three other randomized placebo-controlled studies have also demonstrated that desloratadine significantly improves nasal and ocular symptoms in patients with perennial AR [60,61] and improves quality of life in patients with persistent AR [62].

In a recent meta-analysis, 57 randomized, double-blind, controlled trials were analyzed, and 13 studies were selected, including a total of 3108 subjects. This meta-analysis demonstrated that desloratadine was associated with a significant reduction in total symptom scores (standard mean difference [SMD]: -1.79; 95% CI: -3.10 to -0.47; $p = 0.008$) and total nasal symptom scores (SMD: -0.66; 95% CI: -0.91 to -0.42; $p < 0.001$) compared with placebo. Combined data from seven studies including 438 subjects showed that desloratadine also improved nasal obstruction compared with placebo (SMD: 0.32; 95% CI: 0.10 to 0.55, $p = 0.005$). The efficacy of desloratadine was found to be similar to fexofenadine and levocetirizine in this meta-analysis, although the studies included were uniformly small in size. Concerning inflammatory markers, desloratadine was associated with an improvement in nasal eosinophilia, but not in nasal IL-4 [63].

The activity of desloratadine was compared with other antihistamines in a number of studies. Lee *et al.* compared the relative efficacy of usual clinically recommended doses of desloratadine,

fexofenadine and levocetirizine in patients with perennial AR using nasal provocation challenge and found them to be equally effective in attenuating the response to nasal AMP challenge [64]. Passalacqua *et al.* compared the effects of a single dose of desloratadine and levocetirizine in the nose and skin over 24 h. They found single doses of desloratadine and levocetirizine had a comparable effect on nasal symptoms, but levocetirizine was faster and displayed a greater effect on histamine wheal [65]. Passalacqua *et al.* reviewed eight well-controlled trials that directly compared the effects of levocetirizine and desloratadine in the skin and nose of healthy individuals and patients with AR. Drug activity was measured in terms of wheal, flare and itch reactions; nasal symptoms or symptom scores; increases in concentrations of inflammatory markers; or facial thermography. In most of these trials, levocetirizine had a faster onset and greater consistency of effect than desloratadine [66].

Recently, a number of studies investigated the efficacy of the combined use of antihistamines with leukotriene receptor antagonists (LTRAs). Combined use of desloratadine with LTRAs was reported to be superior to either agent alone in the treatment of persistent AR [67]. Another study also revealed that desloratadine plus montelukast inhibited early asthmatic response after allergen inhalation significantly greater than the inhibition with a LTRA alone [68].

Efficacy of desloratadine in patients with chronic idiopathic urticaria

Urticarial symptoms in CIU are largely mediated by histamine; therefore, patients with CIU also experience marked relief of symptoms upon treatment with antihistamines [7]. To date, desloratadine has been evaluated in six randomized, placebo-controlled trials in patients with CIU. The results are demonstrated in TABLE 2. Overall, desloratadine improved the severity of pruritis, the number of hives and quality of life issues, including sleep disturbances associated with CIU, with a favorable safety profile. No serious adverse events were reported in these studies, with no clinically relevant ECG changes or cardiovascular parameters. One trial in healthy nonatopic adults demonstrated that inhibition of the response to histamine injection was greater with ebastine compared with desloratadine [69]. Frossard *et al.* revealed that levocetirizine suppressed the cutaneous allergic reactions with a higher potency than desloratadine, which correlated with its high receptor occupancy. They suggested that receptor occupancy rather than drug affinity or plasma half-life was more representative of antihistamine potency [70].

Desloratadine monotherapy or combination therapy was also found to be beneficial in other types of urticaria, including cold urticaria [71] or delayed pressure urticaria [72].

Postmarketing surveillance

Glass *et al.* reported a cross-sectional survey (n = 10,023) delivered online to a sample of allergy sufferers in the USA. They compared patients who were dissatisfied with loratadine and converted to either desloratadine (n = 61) or to fexofenadine (n = 211) in terms of satisfaction measures, including side effects associated with the medication, satisfaction with symptom relief and overall satisfaction. On average, patients who were dissatisfied with loratadine reported equal or better satisfaction with desloratadine as fexofenadine. When severity of disease was controlled for in the analysis, a pattern emerged suggesting greater levels of satisfaction amongst loratadine-dissatisfied patients who converted to desloratadine [73].

In a large postmarketing surveillance study in Germany evaluating the safety and efficacy of desloratadine in patients with seasonal allergic rhinitis, 91% of the patients and 93% of the physicians rated desloratadine efficacy as good/excellent. Global safety/tolerability was rated as good/excellent by 98.9% of physicians and 98.5%

Table 1. Pharmacological and clinical characteristics of desloratadine.

Licensed indications	Allergic rhinitis Urticaria
Mechanism of action	Histamine H1 receptor antagonist
Dosage and administration	5 mg, once daily, oral route
Metabolism	Metabolized to 3-hydroxydesloratadine, subsequently undergoes glucoronidation. Excreted in urine and in feces in equal proportions as metabolic products.
Elimination half-life	27 h
Drug interactions	None
Adverse effects	Headache, dry mouth, fatigue, pharyngitis

Table 2. Randomized, placebo-controlled studies of desloratadine in CIU.

Study	Study drugs	Outcome	Ref.
Grob *et al.* (2008)	Desloratadine 5 mg/day 6 weeks vs placebo	Significantly greater improvements compared with placebo in Dermatology Life Quality Index overall score	[87]
Ortonne *et al.* (2007)	Desloratadine 5 mg/day 6 weeks vs placebo	Significant improvements in pruritus scores and in the size of the largest wheals with desloratadine	[75]
Ring *et al.* (2001)	Desloratadine 5 mg/day 6 weeks vs placebo	Desloratadine significantly improved the total CIU symptom score, as well as pruritus, the number of hives and the size of the largest hive	[88]
Monroe *et al.* (2003)	Desloratadine 5 mg/day 6 weeks vs placebo	Desloratadine significantly improved the total CIU symptom score, as well as pruritus, the number of hives and the size of the largest hive	[76]
Di Lorenzo *et al.* (2004)	Desloratadine 5 mg/day 6 weeks vs montelukast 10 mg/day vs desloratadine plus montelukast vs placebo	The groups treated with desloratadine as monotherapy or combined therapy showed significant differences in terms of total symptom score, number of hives and size of the largest hive	[89]
Nettis *et al.* (2004)	Desloratadine 5 mg/day 6 weeks vs desloratadine plus montelukast vs placebo	Desloratadine alone and desloratadine plus montelukast yielded improvements in pruritus, number of separate episodes, size and the number of wheals	[90]

CIU: Chronic idiopathic urticaria.

of patients, and the adverse event rate was very low (0.44%). Mean nasal, ocular, asthma, dermal and total symptom sum scores were reduced significantly during desloratadine treatment compared with baseline ($p = 0.0001$) [74].

Safety & tolerability

Desloratadine is well tolerated and most adverse events reported are mild-to-moderate and experienced by a small proportion of the patients. Adverse effects occurring more frequently than placebo reported in 2% or more of the patients 12 years of age and older having AR (n = 2834) include pharyngitis (4.1 vs 2.0%), dry mouth (3.0 vs 1.9%), myalgia (2.1 vs 1.8%), fatigue (2.1 vs 1.2%), somnolence (2.1 vs 1.80%) and dysmenorrhea (2.1 vs 1.6%). The frequency and magnitude of laboratory and electrocardiographic abnormalities were similar in desloratadine and placebo-treated patients. There were no differences in adverse events for subgroups of patients as defined by gender, age or race [9].

Among patients with CIU, adverse events occurred with similar frequency among desloratadine- and placebo-treated patients [75]. No life-threatening or serious adverse events or deaths occurred. The most frequently reported adverse events in the desloratadine group and placebo were headache (15.5 vs 10%), nausea (6.0 vs 1.8%) and dry mouth (5.2 vs 4.5%) [76].

Two double-blind, randomized, placebo-controlled trials evaluating desloratadine efficacy and safety in 231 children of 2–11 years of age [77] and 255 children of 6–24 months of age showed a similar side-effect profile between the desloratadine and placebo groups [78]. Corresponding doses were 1 mg for 6 to 12 month olds and 1.25 mg for 12 to 24 month olds. Subjects aged between 2 and 5 years were randomly assigned to receive once a day either of desloratadine syrup 1.25 mg (0.5 mg/ml) or placebo, and subjects aged between 6 and 11 years were randomly assigned to receive either desloratadine syrup 2.5 mg once a day or placebo. Adverse effects reported more frequently than placebo among patients between 2 and 5 years of age include fever, urinary tract infection and varicella. Other infrequent side effects in younger children include fever, diarrhea, somnolence, coughing and upper respiratory tract infection [101].

Sedation & CNS impairment

First-generation antihistamines contain aromatic rings and alkyl substitutes that make them lipophilic, explaining their ability to cross the blood–brain barrier, thus causing a variety of unwanted CNS effects, such as sedation and reduced cognitive function [79].

A number of randomized, placebo-controlled studies have confirmed that desloratadine does not impair cognitive functions in therapeutic doses, contrary to other first-generation antihistamines. In one study, desloratadine at higher than recommended doses (20 mg) was found to increase drowsiness and CNS impairment when compared with placebo [80]. In another study that included cohorts comprised of greater than 24,000 patients in total, the incidence of first reports of drowsiness/sedation for levocetirizine or desloratadine was low (46 [0.37%] and 9 [0.08%], respectively) and statistically different ($p < 0.0001$). Reported rates of drowsiness and sedation are low for both drugs; patients

prescribed levocetirizine are more likely to experience drowsiness and sedation in the first month of observation (after starting treatment) than patients prescribed desloratadine [81].

Scharf *et al.* showed that the effect of desloratadine on cognitive functions was not significantly different from placebo as assessed by maintenance of the wakefulness test and multiple sleep latency test, whereas diphenhydramine significantly impaired performance tests [82]. Nicholson *et al.* compared the effects of desloratadine on psychomotor performance, daytime sleep latencies, subjective sleepiness and memory with promethazine on nine volunteers. Desloratadine was found to have no adverse effects [83]. Wilken *et al.* showed that among 248 patients with seasonal AR randomly assigned to take desloratadine, diphenhydramine or placebo, diphenhydramine significantly impaired CNS functions and increased sleepiness, while desloratadine or placebo had no effect [84]. No CNS-related adverse effects were observed in driving performance or performance during flying in-flight simulators after administration of desloratadine [85]. Furthermore, a single dose of desloratadine does not potentiate alcohol-mediated CNS impairment. Desloratadine alone or in combination with alcohol was safe and well tolerated in adult patients [86].

Cardiovascular effects

Many studies evaluating the cardiovascular effects of desloratadine showed that desloratadine was not associated with cardiovascular toxicity [14]. In a double-blind, placebo-controlled study, desloratadine 45 mg administered to 24 healthy volunteers for 10 days with no clinically relevant changes in ECG or other cardiovascular parameters, including QTc interval prolongation, were observed [83]. Another placebo-controlled study including 1026 patients randomly assigned desloratadine (2.5, 5, 7.5, 10 or 20 mg) once-daily for 2 weeks showed no change in baseline ECGs and QTc intervals [47]. The lack of cardiac toxicity seems to be related to the fact that desloratadine does not suppress the cardiac human ether-a-go-go related gene (*HERG*) potassium channel, expressed in Xenopus oocytes [12].

Pregnancy & lactation

Desloratadine had no effect on pup development at an oral dose of 3 mg/kg/day (estimated desloratadine and desloratadine metabolite exposures were approximately seven times the AUC in humans at the recommended daily oral dose). However, there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, desloratadine should be used during pregnancy only if clearly needed.

Desloratadine passes into breast milk; therefore a decision should be made as to whether to discontinue nursing or to discontinue desloratadine, taking into account the importance of the drug to the mother [101].

Regulatory affairs

Desloratadine has been approved for the relief of the nasal and non-nasal symptoms of seasonal and perennial AR, as well as the symptomatic relief of pruritus, reduction in the number of hives, and reduction in the size of hives in patients with CIU in patients 6 months of age or older. It has also been approved in the European Union (EU) for the relief of symptoms associated with AR and urticaria (the label in the EU has recently been expanded to 'urticaria' from CIU for patients >1 year of age). Orodispersible tablets have the same indications/age range as the plain tablets. A desloratadine/pseudoephedrine sulfate combined formulation has been approved in the USA for the relief or nasal and non-nasal symptoms of seasonal AR, including nasal congestion, in patients 12 years of age and older.

Conclusion

Allergic rhinitis and urticaria are common allergic disorders that affect many people all over the world. Second-generation antihistamines are the cornerstone of treatment for AR according to the guidelines. One of these agents is desloratadine, which is a H1 receptor antagonist that is effective in the treatment of nasal and non-nasal symptoms of AR, as well as urticaria. Desloratadine is well-tolerated and has a favorable toxicity profile; it is a nonsedative antihistamine with little or no drug interactions, and it did not show any cardiac adverse events in clinical trials. In addition to its antihistaminic effects, emerging data on novel mechanisms of action considering the anti-inflammatory pathways will improve our understanding and may expand the utility of the drug in allergic disorders.

Executive summary

- Desloratadine is a potent highly selective H1 receptor antagonist that is an active metabolite of loratadine.
- Since desloratadine does not pass the blood–brain barrier, it does not elicit impairment in cognition or motor performance, unlike some other second-generation antihistamines.
- Desloratadine is well tolerated and most adverse events reported are mild/moderate and experienced by a small proportion of the patients.
- Besides effects on H1 receptors, desloratadine also possesses anti-inflammatory activity. It reduces the release of anti-inflammatory cytokines and other mediators involved in early- and late-phase allergic response.
- Desloratadine has been shown to inhibit expression of cell-adhesion molecules, and release of preformed histamine from mast cells and basophils following allergen challenge.
- Desloratadine provides relief of allergic rhinitis symptoms, including nasal congestion, quickly after the first dose.
- With its relatively long elimination half-life and rapid onset of action, the drug is suitable for once-daily dosing.
- Desloratadine is not associated with cardiovascular toxicity, including QTc interval prolongation or cardiac arrythmia. The lack of cardiac toxicity seems to be related to the fact that desloratadine does not affect cardiac potassium channels.
- Desloratadine causes no clinically relevant pharmacodynamic or electrocardiographic interactions when co-administered with inhibitors of major CYP isoenzymes.
- Many large, randomized, double-blind, placebo-controlled trials have confirmed that desloratadine is effective against symptoms of intermittent and persistent allergic rhinitis.
- Patients with chronic idiopathic urticaria also experience marked relief of symptoms upon treatment with desloratadine, since urticarial symptoms in chronic idiopathic urticaria are largely mediated by histamine.

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Website

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