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Loratadine and Desloratadine Use in Children

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Loratadine is one of the most widely used antihistamines in the United States. Introduced on April 12, 1993 as a prescription medication for the treatment of perennial or seasonal allergic rhinitis and chronic idiopathic urticaria, it is now available without a prescription or "over the counter" (OTC) in a wide variety of formulations.^{1,2} Desloratadine, the single active isomer of loratadine, was approved by the Food and Drug Administration (FDA) on December 21, 2001 and still requires a prescription.^{3,4} Both versions are approved for pediatric use: loratadine for children as young as 2 years of age and desloratadine for infants 6 months of age and older. This issue of *Pediatric Pharmacotherapy* will provide a brief review of loratadine and desloratadine, focusing on studies supporting their use in the pediatric population.

Mechanism of Action

Loratadine is a long-acting tricyclic second-generation antihistamine. It is an antagonist at peripheral histamine (H₁) receptors. Desloratadine (descarboethoxyloratadine) is the active metabolite of loratadine and produces the same pharmacologic effect as the parent compound. An oral dose of loratadine or desloratadine typically begins to inhibit the wheal and flare reaction after intradermal histamine injection within 1-3 hours, reaches a peak effect within 8-12, and lasts for approximately 24 hours. As with other second-generation antihistamines, neither drug crosses the blood-brain barrier in significant quantities to produce central nervous system (CNS) effects. While up to 100% of central H₁ receptors may be occupied by first-generation antihistamines, the second-generation agents typically occupy only 20% of these receptors.^{1,4}

Pharmacokinetics

Both loratadine and desloratadine are rapidly absorbed after oral administration. Loratadine reaches maximum concentrations in 1-1.5 hours, compared to 3 hours for desloratadine. Food

does not significantly alter absorption. Both compounds are highly protein bound (80-90%).

Loratadine is metabolized via cytochrome P450 3A4 (CYP3A4) and to a lesser extent by CYP2D6. The major metabolite of loratadine, desloratadine, is metabolized to 3-hydroxydesloratadine. This compound then undergoes glucuronidation prior to excretion. The mean elimination half-lives of both loratadine and desloratadine are approximately 27-28 hours in healthy adults. It has been estimated that up to 6% of the population are poor metabolizers of desloratadine, having a half-life of more than 50 hours. Hepatic dysfunction also extends the half-lives of both drugs in adults.²⁻⁴

The pharmacokinetic profiles of both loratadine and desloratadine have been studied in children and appear similar to values found in adults. In 1995, Lin and colleagues studied the pharmacokinetics of loratadine in 14 children between 8 and 12 years of age.⁵ The children weighing less than 30 kg received a single dose of 5 mg loratadine syrup and those weighing more than 30 kg were given a 10 mg dose. The mean loratadine peak concentration of 4.38 ng/mL occurred at an average of 1 hour after administration. The average peak desloratadine concentration, 3.79 ng/mL, was reached at 1.69 hours. While the elimination half-life for loratadine was not evaluated, the average half-life for desloratadine was 13.8 hours.

In 2000, Salmun and colleagues studied loratadine pharmacokinetics in children between 2 and 5 years of age.⁶ In their open-label study, 18 children received a single 5 mg dose of loratadine syrup. The maximum serum concentrations of loratadine and desloratadine were 7.8 ng/mL and 5.1 ng/mL, respectively. The peak concentration of loratadine occurred at 1.2 hours, with a desloratadine peak at 2.3 hours, similar to the results observed in older children.

The pharmacokinetic profile of desloratadine has been studied by Gupta and colleagues in both infants and children. In their 2006 paper published in the *British Journal of Clinical Pharmacology*, the authors described the results of two open-label single-dose studies, one in 18 children 2-5 years of age and one in 18 children 6-11 years of age.⁷ The younger children received 1.25 mg of desloratadine syrup and the older subjects were given 2.5 mg. In both groups, maximum desloratadine concentrations occurred at 2 hours after dosing. The average elimination half-life was 16.4 ± 13.9 in the younger children and 19.4 ± 15.8 hours for the older group.

In a separate study, Gupta and colleagues used a population pharmacokinetic analysis to evaluate desloratadine in 58 infants and children between 6 months to 2 years of age.⁸ Subjects were randomly assigned to either a 0.625 mg or 1.25 mg dose of desloratadine syrup. The mean peak desloratadine concentrations were 1.69 ng/mL in the patients less than 1 year of age and 1.56 ng/mL in the patients 1-2 years of age. The time to reach maximum concentration was similar in the two groups: 3.16 hours in the infants and 3.1 hours in the 1-2 year olds). The estimated elimination half-life was 14.6 hours in the infants and 12.4 hours in the 1-2 year old group. The results of these three studies establish the similarity in pharmacokinetic characteristics of desloratadine in infants, children, and adults.

Clinical Trials

In 1989, Boner and colleagues compared the efficacy and safety of loratadine to standard therapy with a first-generation antihistamine in 40 children with allergic rhinitis.⁹ Patients were randomized to receive either loratadine (2.5 or 5 mg once daily, equivalent to 0.11-0.24 mg/kg, once daily) or dexchlorpheniramine (0.1-0.23 mg/kg every 8 hours) for 14 days. Nasal discharge, congestion, and nasal itching, as well as itching, burning, or watery eyes and itching of the ears or palate were evaluated at days 3, 7, and 14. Both drugs significantly reduced nasal and ocular symptoms compared to baseline throughout the duration of the study ($p < 0.01$). While both drugs were well tolerated overall, only the children in the dexchlorpheniramine group experienced drowsiness.

These investigators published another pediatric loratadine study in 1992, comparing loratadine (5 or 10 mg once daily) and astemizole (0.2 mg/kg once daily).¹⁰ Forty-one children (6-14 years of age) were enrolled in the 14-day blinded study.

Significant improvement in allergy symptoms was reported in both groups, with a response of excellent or good in 83.3% of the loratadine patients and 58.8% of the astemizole group.

Lutsky and colleagues compared loratadine and terfenadine in an international study of 96 3-6 year old children with allergic rhinitis.¹¹ Patients were randomized to receive loratadine (5 or 10 mg once daily) or terfenadine (15 mg twice daily) for 14 days. Mean scores for nasal and non-nasal allergy symptoms were significantly reduced from baseline in both groups ($p < 0.05$) at days 3, 7, and 14. Non-nasal symptoms were more likely to improve with loratadine ($p < 0.05$). Therapeutic response was rated as excellent or good in 82% of the loratadine patients and 60% of the terfenadine group.

The first published report of desloratadine in children was a tolerability study conducted by the manufacturer. Bloom and colleagues performed a double-blind, placebo-controlled trial in 111 children between 2 and 5 years of age and 129 children 6 to 11 years of age.¹² Desloratadine doses were 1.25 mg in the younger group and 2.5 mg in the older children. There were no significant differences in the incidence of minor adverse effects between active drug and placebo in either age group. No serious or severe adverse event were reported. Electrocardiogram (ECG) results showed no significant changes.

In 2005, Rossi and coworkers described the first clinical efficacy trial of desloratadine in children.¹³ A total of 54 children (6-12 years of age) were enrolled in their 4-week open-label trial. The patients received 2.5 mg desloratadine syrup once daily. Rhinorrhea, sneezing, nasal congestion, cough, ocular symptoms, and itching were significantly reduced during the study. In the children with underlying asthma, the use of short-acting beta₂-adrenergic agonists was also reduced. There only adverse effects reported were one case each of insomnia and diarrhea.

The safety of desloratadine was evaluated in children 6 months to 2 years of age by Prenner and colleagues in 2006.¹⁴ Two hundred fifty-five children were randomized to either desloratadine (1 or 1.25 mg once daily, depending on age) or placebo for 15 days. The most commonly reported adverse effects were somnolence (in 5.3% of desloratadine and 7.3% of controls), diarrhea (6.1% and 2.4%, respectively), and irritability (6.9% and 5.6%, respectively). There were no significant changes in ECG parameters and no serious or severe adverse effects.

In 2007, Dizdar and colleagues compared regular and intermittent “as needed” desloratadine administration in 37 adolescents (ages 12-18 years) with allergic rhinitis.¹⁵ Patients were randomized to a regimen of 10 mg desloratadine each morning for 4 weeks or 10 mg daily on an as needed basis. There were no differences between the groups in symptom control. Inflammatory markers and nasal flow measurements were also no different. Albuterol use was lower in the regular desloratadine group during the fourth week of the study, when pollen counts were high. No adverse effects were reported. The authors concluded that intermittent administration was adequate for most children with allergic rhinitis, but that regular administration may provide better control for children with airway reactivity.

Contraindications and Precautions

Loratadine and desloratadine are contraindicated in patients with a known sensitivity to either drug or the excipients used in the formulations available. Hypersensitivity reactions are rare, but include rash, urticaria, pruritus, dyspnea, edema, and anaphylaxis.²⁻⁴ Although some earlier second-generation antihistamines (astemizole, terfenadine) have been associated with prolongation of the QTc interval and a risk for torsades de pointes, multiple studies have shown no effect on ECG parameters by loratadine or desloratadine.^{2-4, 6, 8, 12, 14}

Adverse Effects

Both loratadine and desloratadine are well tolerated in children.^{6, 9-15} Loratadine adverse effects were monitored in premarketing trials involving approximately 300 children between 6 and 12 years of age, with the most frequently reported events including abdominal pain (2% of treated patients vs. 0 placebo controls), fatigue (3% vs. 2%), hyperkinesia (3% vs. 1%), malaise (2% vs. 0), nervousness and wheezing (both 4% vs. 2%), and conjunctivitis, dysphonia, and upper respiratory tract infection (2% vs. < 1%). Sixty children between 2 and 5 years of age were also studied as part of a 2-week double-blinded, placebo-controlled clinical trial. The most common adverse effects were diarrhea and epistaxis (3% vs. 0 controls), pharyngitis (3% vs. 2%), earache, fatigue, influenza-like symptoms, rash, stomatitis, tooth disorder, and concomitant viral infection (all 2% vs. 0).² Diarrhea associated with loratadine or desloratadine solutions may be caused by the sorbitol in these products.

The adverse effects of desloratadine were studied by the manufacturer in three placebo-controlled clinical trials of 246 children between 6 months and 11 years of age. In the oldest children (those between 6 and 11 years of age), there were no adverse effects reported in more than 2% of patients. In the 2-5 year old group, the most common reactions were fever (5.5% of children given desloratadine vs. 5.4% of controls), urinary tract infection and concomitant varicella infection (3.6% vs. 0). In the patients between 12 and 23 months of age, the most frequent adverse effects were fever (16.9% vs. 12.9%), diarrhea (15.4% vs. 11.3%), upper respiratory tract infections (10.8% vs. 9.7%), coughing (10.8% vs. 6.5%), increased appetite (3.1% vs. 1.6%), and emotional lability, epistaxis, parasitic infection, pharyngitis, and rash (all 3.1% vs. 0).⁴

In infants, the most common reactions were upper respiratory tract infections (21.2% vs. 12.9%), diarrhea (19.7% vs. 8.1%), fever (12.1% vs. 1.6%), irritability (12.1% vs. 11.3%), coughing (10.6% vs. 9.7%), somnolence (9.1% vs. 8.1%), bronchitis (6.1% vs. 0), otitis media (6.1% vs. 1.6%), vomiting (6.1% vs. 3.2%), anorexia (4.5% vs. 1.6%), pharyngitis (4.5% vs. 1.6%), insomnia (4.5% vs. 0), rhinorrhea (4.5% vs. 3.2%), erythema (3% vs. 1.6%) and nausea (3% vs. 0). None of the patients had a significant change in ECG measurements. Only one patient required discontinuation of treatment.⁴

Drug Interactions

Drugs that inhibit the activity of CYP3A4, such as erythromycin, cimetidine, and ketoconazole, prolong the metabolism of loratadine and desloratadine. As a result, plasma concentrations may increase significantly. Administration of ketoconazole 200 mg every 12 hours produced a 307% increase in loratadine plasma concentrations, measured as the area under the concentration-time curve over 24 hours, and a 39% increase in desloratadine concentrations. In spite of the increase in plasma concentrations, studies conducted in healthy adult volunteers have not revealed a change in vital signs, electrocardiographic measurements of the QTc interval, laboratory tests, or other adverse effects. Azithromycin and fluoxetine may also increase loratadine or desloratadine concentrations, but to a lesser degree.²⁻⁴

Dosing Recommendations

The recommended dose for loratadine in children 2-5 years of age is 5 mg given orally once daily. For children 6 years of age or older and adults, the recommended dose is 10 mg once daily or 5

mg every 12 hours. For patients above the age of 6 with renal or hepatic dysfunction, a 10 mg dose should be administered every other day rather than daily.²⁻⁴

The FDA-approved dosing for desloratadine in children between 6 to 11 months of age is 1 mg given orally once daily. For children 1 to 5 years of age, the dose is 1.25 mg once daily. The dose for children 6 to 11 years of age is 2.5 mg once daily. Patients 12 years of age and older may take 5 mg once daily. Adults with renal or hepatic impairment should take 5 mg every other day; dosing for younger patients has not been established. Both loratadine and desloratadine may be taken with or without food.²⁻⁴

Availability

Loratadine is sold OTC as Claritin[®] (Schering) and numerous generic brands. It is available as 10 mg tablets and capsules, 5 and 10 mg dispersible tablets, a 5 mg chewable tablet, and a 1 mg/mL syrup. Desloratadine (Clarinx[®], Schering) is available as a 5 mg tablet, 2.5 and 5 mg dispersible tablets, and a 0.5 mg/mL syrup. The dispersible tablets may be taken with or without water. Families of patients with phenylketonuria should be aware that many of these products contain phenylalanine.²⁻⁴

Summary

Loratadine and desloratadine are effective therapies for the management of seasonal or perennial allergic rhinitis and urticaria in infants, children, and adults. As with other second generation antihistamines, their decreased potential for causing sedation compared to older agents, make loratadine and desloratadine first-line therapies for pediatric patients with allergies.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 4/22/11:

1. Sevelamer carbonate (Renvela[®]) was added to the Formulary for management of hyperphosphatemia. Sevelamer HCl (Renagel[®]) was deleted.
2. Acetaminophen injection (Ofirmev[™]) was added to the Formulary. After an order has been active for 24 hours, it may be changed to oral acetaminophen by a clinical pharmacist if the patient is taking other oral medications. For patients not taking oral medications after 24 hours, a clinical pharmacist will discuss plans for continuing IV acetaminophen with the prescriber. For more information, refer to: <http://www.healthsystem.virginia.edu/alive/pediatrics/PharmNews/201104.pdf>
3. Moisture barrier ointment with miconazole 2% (Critic-Aid[®]) was added for use in adults.

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