

# PEDIATRIC PHARMACOTHERAPY

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## Cetirizine and Levocetirizine Use in Children

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The second generation antihistamines, cetirizine, loratadine, and fexofenadine, were introduced in the United States between 1994 and 1996. Since that time, they have become first-line therapy for the management of allergic rhinitis and urticaria in adults and children.<sup>1</sup> Compared to first generation antihistamines, these agents produce significantly less sedation. The commercial success of cetirizine, as well as its subsequent transition to non-prescription or "over-the-counter" (OTC) status, prompted the release of a single-isomer derivative, levocetirizine, on May 25, 2007.<sup>2-5</sup> Both cetirizine and levocetirizine are approved by the Food and Drug Administration for use in children 2 years of age and older. This issue of *Pediatric Pharmacotherapy* will focus on cetirizine and levocetirizine, reviewing their basic pharmacology and discussing current studies describing their use in children.

### Mechanism of Action

Cetirizine is a metabolite of hydroxyzine, a first generation piperazine antihistamine. It produces selective inhibition of peripheral histamine (H<sub>1</sub>) receptors. Cetirizine has minimal anticholinergic or antiserotonergic activity and has limited penetration into the brain. At doses of 5 to 10 mg, it strongly inhibits wheal and flare reactions after intradermal histamine injection in both children and adults. Levocetirizine is the active R enantiomer of cetirizine. It has an affinity for H<sub>1</sub> receptors approximately 2-fold higher than racemic cetirizine. At a dose of 5 mg, levocetirizine inhibits wheal and flare reactions in children and adults for up to 24 hours.<sup>1-5</sup>

### Pharmacokinetics

Both cetirizine and levocetirizine are rapidly and extensively absorbed after oral administration. The average time to maximum plasma concentrations is approximately 1 hour. Administration with food reduces peak concentrations and delays the time to achieve the peak concentrations, but does not affect the extent of drug exposure, as measured by area under the concentration curve (AUC) values.<sup>3-5</sup>

Cetirizine and levocetirizine are highly (91-93%) protein bound. They can cross the blood-brain barrier, but typically occupy only 30-50% of the H<sub>1</sub> receptors in the cerebral cortex, compared to more than 90% of peripheral H<sub>1</sub> receptors. Approximately 50 to 80% of a cetirizine or levocetirizine dose is excreted in the urine as unchanged drug. Remaining drug undergoes aromatic oxidation and N- and O-dealkylation in the liver to inactive compounds. The average elimination half-life of both drugs is 8 to 9 hours in adults. Cetirizine and levocetirizine are excreted by glomerular filtration and active tubular secretion; their clearance correlates with creatinine clearance. Renal impairment reduces their clearance.<sup>3-5</sup>

In a cetirizine pharmacokinetic trial conducted by the manufacturer in children between 7 and 12 years of age, the weight-normalized total body clearance after a 5 mg dose was 33% greater than values observed in adults and the elimination half-life was 33% shorter.<sup>3</sup> Children 2 to 5 years of age who received a 5 mg dose had a total body clearance 81 to 111% greater than that of adults and an elimination half-life that was 33 to 41% shorter.

A similar increase in clearance was observed in a levocetirizine trial conducted in 14 children between 6 and 11 years of age.<sup>4,5</sup> After a 5 mg dose, the average maximum serum concentration and AUC values were approximately 2-fold greater than those in adults. Total body clearance was 30% greater and elimination half-life was 24% shorter than values reported in adults. Although prospective pharmacokinetic trials have not been conducted in younger patients, the manufacturer states that data from a retrospective population pharmacokinetic study in 324 children and adults suggest that children 6 months to 5 years of age given a dose of 1.25 mg once daily achieve plasma levocetirizine concentrations similar to those of adults receiving a 5 mg dose.

## Clinical Trials

### *Efficacy*

The efficacy of cetirizine has been established in several studies. In 2000, Simons and colleagues conducted a prospective, randomized, placebo-controlled, double-blind, cross-over single-dose study to evaluate the onset and duration of action of cetirizine and loratadine.<sup>6</sup> Fifteen children (mean age 9 years) underwent testing. Cetirizine, at a dose of 10 mg, suppressed the wheal and flare reaction from 0.25 to 24 hours after dose administration. A 10 mg dose of loratadine produced suppression of response from 0.75 to 24 hours. The authors concluded that both agents were effective antihistamines for children.

The efficacy of both drugs was also recently evaluated in a randomized, double-blind, placebo-controlled trial in children 6 to 12 years of age.<sup>7</sup> Eighty children with moderate to severe perennial allergic rhinitis were enrolled and randomized to receive either cetirizine (10 mg), levocetirizine (5 mg), or placebo daily at bedtime for 12 weeks. Nasal symptoms consisting of rhinorrhea, congestion, itching, and sneezing, in addition to non-nasal symptoms consisting of eye itching or burning, tearing, eye redness, or itching of the ears or palate were recorded each day by the patient or a parent. The eight symptoms were combined to make a total symptom score (TSS). Patients were evaluated at 4, 8, and 12 weeks. Families also completed quality of life questionnaires. All patients underwent nasal peak expiratory flow rate (nPERF) assessments and laboratory testing for eosinophil counts and IgE levels. Nasal smears were also examined for eosinophils.

Both cetirizine and levocetirizine produced significantly greater improvements in TSS than placebo. Cetirizine appeared to be more efficacious than levocetirizine with statistically significant differences in scores at weeks 8 and 12. Questionnaire results were significantly better in the treatment groups compared to placebo, but there was no difference between the two antihistamines. Both cetirizine and levocetirizine improved nPERF values compared to placebo, with cetirizine producing a greater effect. The eosinophil proportion in nasal smears decreased in the cetirizine group, but not in the other groups. The authors concluded that both drugs were effective in improving symptoms in children with allergic rhinitis, but that cetirizine appeared to be more efficacious.<sup>7</sup>

Similar benefit in allergic symptoms was observed in two prospective randomized, double-

blind, placebo-controlled trial of cetirizine in children.<sup>8,9</sup> de Blic and colleagues used a four item symptom score (T4SS), which includes sneezing, rhinorrhea, nasal and ocular pruritus, to evaluate the efficacy of 5 mg levocetirizine given daily versus placebo in 177 children between 6 and 12 years of age.<sup>8</sup> The authors found significant improvement in T4SS in the treatment group, with a difference in adjusted means of 1.29 (95% CI, 0.66-1.92). Potter and colleagues, publishing as the Pediatric Levocetirizine Study Group, found similar results in their study of 306 children between 6 and 12 years of age.<sup>9</sup> Patients received either 5 mg levocetirizine once daily or placebo for 4 weeks. T4SS, 50% response rate, quality of life questionnaire scores, and the investigators' global evaluations of improvement were significantly better in the treatment group.

### *Safety*

An 18-month prospective, randomized, double-blind study established the long-term safety of cetirizine in children.<sup>10</sup> The Early Treatment of the Atopic Child (ETAC) study randomized 817 children (1-2 years of age) to either 0.25 mg/kg cetirizine or placebo given twice daily. The most frequent reactions were insomnia, somnolence, and fatigue. There were no significant differences in the rate of these adverse effects between the groups. No adverse effects on growth, behavioral, or developmental assessments were reported, and there were no abnormalities noted on laboratory tests or electrocardiograms.

The safety of long-term levocetirizine use in young children was also studied by the Early Prevention of Asthma in Atopic Children (EPAAC) Study Group in 2007.<sup>11</sup> This prospective, randomized, double-blind placebo-controlled trial enrolled 510 atopic children between 12 and 24 months of age. Patients were randomized to receive either 0.125 mg/kg levocetirizine or placebo twice daily for 18 months. The frequency of serious adverse effects was similar between the two study arms (12.2% in the levocetirizine group and 14.5% in the controls). The incidence of medication-attributed adverse effects was also similar between groups (5.1% in the levocetirizine group and 6.3% in the controls). Two percent of the levocetirizine patients withdrew from the study because of adverse effects compared to 1.2% of the children in the placebo group. The most frequently reported adverse effects were related to upper respiratory tract infections, transient gastrointestinal symptoms, or worsening of

allergic disease. There were no differences between the groups in height, weight, attainment of developmental milestones, or laboratory tests. The authors concluded that long-term administration of levocetirizine was associated with a mild adverse effect profile in young children.

#### Contraindications and Precautions

Cetirizine and levocetirizine are contraindicated in patients with known hypersensitivity to any components of the products or hydroxyzine. Use of levocetirizine is contraindicated in children with renal impairment, adults with end-stage renal disease (defined as a creatinine clearance of less than 10 mL/min), and patients undergoing dialysis.<sup>3-5</sup>

#### Adverse Effects

Cetirizine and levocetirizine are generally well tolerated. As in clinical trials in adults, dose-related somnolence has been the most common adverse effect reported in pediatric trials. Although the incidence is significantly lower with these agents than with the first generation antihistamines, it is still relatively common, especially during the first days of treatment. In pre-marketing trials of cetirizine, the incidence of somnolence was 1.9% in children given 5 mg and 4.2% in those given 10 mg, compared to a rate of 1.3% in the placebo group.<sup>3-5</sup> Patients and/or parents should be aware of the risk for somnolence with antihistamine use and take proper precautions when the patient will be involved in activities requiring alertness.

Other common adverse effects of cetirizine and levocetirizine in pediatric clinical trials have been nasopharyngitis (2% with cetirizine, 4-6% with levocetirizine, and 2-3% in controls) and dry mouth (5% with cetirizine, 2-3% with levocetirizine, and 1-3% in controls). Fever, cough, epistaxis, abdominal pain, nausea, vomiting, and diarrhea were reported in 5% of patients or less. Discontinuation of cetirizine due to adverse reactions has been uncommon in pediatric trials, occurring in 0.4% of patients given cetirizine and 1% of the placebo controls. Likewise, only 0.5% of children in levocetirizine clinical trials have withdrawn because of adverse effects.<sup>3-5</sup>

Cetirizine has been associated with the development of dystonic reactions and oculogyric crisis in a small number of cases. This may be related to its ability to block dopamine receptors in the central nervous system, producing an alteration in dopaminergic-

cholinergic balance. In 2006, Rajput and colleagues described a child who developed a dystonic reaction after 18 days of cetirizine administration (5 mg/day).<sup>12</sup> The patient continued to experience symptoms 8 weeks after discontinuation of cetirizine and later developed dystonia after receiving a cough and cold product, suggesting a possible predisposition to dystonia.

A second case of cetirizine-induced dystonia was recently reported in a 6-year-old boy.<sup>13</sup> The patient had been taking cetirizine 5 mg/day for 3 days prior to the onset of involuntary deviation of the jaw to the left and an inability to swallow. The patient was brought to the emergency department where vital signs, laboratory values, and physical examinations were normal. The patient was treated with 5 mg biperidene (a peripheral anticholinergic), with resolution of symptoms within an hour. There was no recurrence of dystonia at follow-up.

#### Drug Interactions

Administration of theophylline at recommended doses may produce a small (<20%) decrease in the clearance of cetirizine. There is a possible risk for increased cetirizine serum concentrations with large doses of theophylline. Ritonavir increases serum concentrations of cetirizine by approximately 40%, slowing clearance and increasing the elimination half-life. Although not studied, the effect of these drugs on levocetirizine may be similar.<sup>3-5</sup>

#### Dosing Recommendations

The recommended dose for cetirizine in adults and children 6 years of age and older is 5 to 10 mg given once daily. Children between 2 and 6 years of age should begin therapy with 2.5 mg of the oral solution taken once daily. If necessary to control symptoms, the dose can be increased to 5 mg once daily or 2.5 mg given every 12 hours.<sup>3-5</sup>

The dose of levocetirizine in adults and children 12 years of age and older is typically 5 mg taken once daily. Some patients may experience satisfactory symptom control with a lower 2.5 mg dose. The recommended dose for children 6 to 11 years of age is 2.5 mg taken once daily, and the dose for children 6 months to 5 years of age is 1.25 mg given once daily. The manufacturer recommends that levocetirizine be taken in the evening. As an alternative, a dose of 0.125 mg/kg may be given twice daily in children less than 2 years of age who do not respond or do not tolerate the once daily regimen. A 2.5 mg dose may be given twice daily in children over 2 years

of age. Both cetirizine and levocetirizine can be taken with or without food.<sup>3-5</sup>

Adults and children over 12 years of age with renal dysfunction should receive a reduced dose. The dose for adults with mild renal impairment is 2.5 mg once daily. For moderate renal impairment, the dose is 2.5 mg every other day, and for severe renal impairment, levocetirizine should be administered no more frequently than every 3 to 4 days. Use in younger children with renal dysfunction is not recommended.<sup>3-5</sup>

#### Availability

Cetirizine (Zyrtec<sup>®</sup> and others) is available as 5 and 10 mg tablets, 5 and 10 mg chewable tablets, 10 mg liquid gels, and a 1 mg/mL oral syrup. It is also sold in a combination product with 5 mg cetirizine and 120 mg pseudoephedrine.<sup>3</sup> All cetirizine products are available without prescription. Levocetirizine (Xyzal<sup>®</sup>) is available by prescription as a 5 mg scored tablet and a 0.5 mg/mL oral solution.<sup>4,5</sup>

#### Summary

Cetirizine and levocetirizine are effective therapies for the management of allergic rhinitis and urticaria in children as well as adults. Their decreased propensity to cause somnolence compared to the first generation antihistamines makes them first-line therapy for most patients.

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#### Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 5/28/10:

1. Japanese encephalitis vaccine (Ixiaro<sup>®</sup>) was added to the Formulary for vaccination of patients 17 years of age and older.
2. Edrophonium (Enlon<sup>®</sup>) was approved for diagnosis of myasthenia gravis and reversal of nondepolarizing neuromuscular blocking agents.
3. Citalopram and immediate-release venlafaxine were also added to the Formulary.
4. Collagenase clostridium histolyticum (Xiaflex<sup>™</sup>) was added for the treatment of Dupuytren's contracture with restriction to approved prescribers.
5. Tobramycin solution for inhalation (TOBI<sup>®</sup>) was approved for management of *Pseudomonas aeruginosa* in patients with cystic fibrosis.
6. Pantoprazole was approved for patients taking clopidogrel, to provide a proton pump inhibitor option with less inhibition of CYP2C19.
7. Ertapenem and zoledronic acid were deleted.

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