Levocetirizine: Pharmacokinetics and pharmacodynamics in children age 6 to 11 years

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Background: The pharmacokinetics and pharmacodynamics of medications may differ between children and adults, necessitating different dose regimens for different age groups. Levocetirizine, the active enantiomer of cetirizine, is used in the treatment of allergic rhinitis and chronic urticaria in Europe. Its pharmacokinetics and pharmacodynamics have not yet been studied prospectively in school-age children.
Objectives: This study was performed to investigate levocetirizine pharmacokinetic disposition and pharmacodynamics in relation to skin reactivity to histamine in children aged 6 to 11 years.
Methods: Blood samples were obtained at predose baseline and at defined intervals up to and including 28 hours after a 5-mg levocetirizine dose. Concurrently, epicutaneous tests with histamine phosphate, 1 mg/mL, were performed. Wheals and flares were traced at 10 minutes, and the areas were measured with a computerized digitizing system.
Results: In children aged 8.6 ± 0.4 years (± SEM), the peak levocetirizine concentration was 450 ± 37 ng/mL, and the time at which peak concentrations occurred was 1.2 ± 0.2 hours. The terminal elimination half-life was 5.7 ± 0.2 hours, the oral clearance was 0.82 ± 0.05 mL/min/kg, and the volume of distribution was 0.4 ± 0.02 L/kg. Compared with predose areas, the wheals and flares produced by histamine phosphate were significantly decreased from 1 to 28 hours, inclusive ($P < .05$). Mean maximum inhibition of wheals and flares occurred from 2 to 10 hours (97% ± 1%) and from 2 to 24 hours (93% ± 1%), respectively.
Conclusions: Levocetirizine had an onset of action within 1 hour and provided significant peripheral antihistaminic activity for 28 hours after a single dose. Once-daily dosing may be optimal in children aged 6 to 11 years, as it is in adults. (J Allergy Clin Immunol 2005;116:355-61.)

Key words: *H_1-antihistamine, levocetirizine, pharmacokinetics, pharmacodynamics, wheal, flare, allergic rhinitis, urticaria, children*

The pharmacokinetics (absorption, distribution, metabolism, and excretion) and pharmacodynamics of many medications, including those used in the treatment of allergic diseases, have not been optimally investigated in the pediatric population.[1] In the absence of such clinical pharmacology data, drug doses and dose intervals have to be extrapolated from those recommended for adults, and the dose and dose interval selected may not be optimally efficacious or safe in children. Indeed, many drug regulatory agencies now mandate clinical pharmacology studies in the pediatric population.[2]

More than 40 H_1-antihistamines are used in the treatment of allergic rhinitis, urticaria, and other diseases.[3] Most of the orally administered H_1-antihistamines are available in dosage formulations suitable for administration to children and even to infants; however, only 11 of the 40 H_1-antihistamines have been studied prospectively in children with regard to their pharmacokinetics and pharmacodynamics.[4-23] These studies have generally been conducted after administration of a single dose,[5-10,12-20] but 3 studies have been performed at steady state,[11,12,20] and in a few studies, a population pharmacokinetic design[21-23] has been used. The clinical pharmacology of a few of the first-generation H_1-antihistamines, such as chlorpheniramine, brompheniramine, diphenhydramine, and hydroxyzine, was investigated after they had been used in children for several decades. In contrast, the pharmacokinetics and pharmacodynamics of the second-generation H_1-antihistamines cetirizine, fexofenadine, ebastine, loratadine, levocetirizine, and mizolastine have been investigated in the pediatric population relatively early in drug development.

In the present study our objective was to characterize the pharmacokinetics and pharmacodynamics of the new H_1-antihistamine levocetirizine in children aged 6 to 11 years. Levocetirizine[24-29] (Fig 1) is the active R-enantiomer of the racemate cetirizine. It is highly selective for the human histamine H_1-receptor, at which it has twice the binding affinity of cetirizine. Levocetirizine has conformational stability and is not converted to dextrocetirizine, the S-enantiomer, which has 30-fold less binding affinity than cetirizine at the H_1-receptor. Levocetirizine is minimally metabolized; during the week after administration of a single oral ^{14}C-labeled dose

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Abbreviations used
EC_{50}: Plasma concentration producing 50% of E_{max}
E_{max}: Maximum effect attributable to medication

to adults, 85.4% and 12.9% of the drug can be recovered unchanged in urine and feces, respectively.[26] Like enantiomers of other medications, levocetirizine is considered to be a new chemical entity, and as such, its pharmacokinetics, pharmacodynamics, efficacy, and safety need to be defined in individuals in various age groups. We hypothesized that in children aged 6 to 11 years, as in adults, it would have prompt onset of action and would also have peripheral H_1-antihistaminic activity lasting at least 24 hours after a single dose.

METHODS

To test the hypothesis stated above, we performed a prospective, open-label, single-dose study of levocetirizine involving objective pharmacokinetic and pharmacodynamic measurements. Approval for levocetirizine administration was obtained through a New Drug Submission to Health Canada. The study protocol was approved by the University of Manitoba Research Ethics Board on the Use of Human Subjects in Research. Before study entry, written assent was obtained from each child, and written informed consent was obtained from the parent or parents of each child.

Selection of participants

Children were eligible to participate if they were 6 to 11 years of age, weighed 20 to 40 kg, and had mild allergic rhinitis. They were excluded if they had any recent acute illness or any other health problem except for mild intermittent or persistent asthma or if they required any oral medication, including any oral H_1-antihistamines, in the week before study entry or during the study. The only medications permitted before and during the study were as follows: low-dose (100 μg) intranasal glucocorticoids for rhinitis and low-dose (≤250 μg) inhaled glucocorticoids and as-needed inhaled albuterol for asthma.

Study outline

During a preliminary visit to the Manitoba Institute of Child Health Pediatric Allergy Laboratory, the children were assessed for their ability to meet the inclusion criteria of the study. Medical history was obtained, and physical examination, complete blood count, urinalysis, and assessment of hepatic and renal function were performed. The children were given the opportunity to become familiar with the test procedures.

In addition to the medication restrictions noted previously, before the levocetirizine dose and for 28 hours afterward, study participants refrained from ingesting methylxanthine-containing substances (eg, cola, chocolate, or cocoa). After an 8- to 10-hour overnight fast, at 8 AM, a single dose of levocetirizine was administered as a 5-mg tablet, followed by 150 mL of water. For the first 1.5 to 2 hours after dosing, only clear juice or water was permitted.

EMLA local anesthetic cream (Astra, Mississauga, ON, Canada) was applied to potential venipuncture sites. An indwelling intravenous catheter (Critikon, Tampa, FL) was inserted, and 2.5-mL blood samples were obtained before dosing and at 0.5, 1, 2, 3, 4, 6, 8, 10, 24, 26, and 28 hours afterward. The first 1 mL of blood was discarded. After each sample was obtained, the catheter was rinsed with 1.5 mL of 0.9% saline. Blood samples were centrifuged at room temperature at 3700 rpm for 10 minutes. The plasma was transferred to polypropylene tubes, which were sealed and frozen at −20°C until measurement of levocetirizine concentrations was performed.[22]

After each blood sample was collected at the times stated above, peripheral H_1-antihistaminic activity was evaluated by one investigator who performed epicutaneous tests with histamine phosphate, 1 mg/mL, on the volar surfaces of the forearms by using sterilized disposable straight needles (Coates & Clark, Greer, SC) and the prick-through drop technique. All skin tests were performed in duplicate. A different site on the volar surfaces of the forearms was used for each skin test. The sequence of test sites was identical in all children.

Analytic methods

Levocetirizine concentrations were determined in plasma samples by using chiral HPLC with tandem mass spectrometric detection after online processing through the column-switching method.[22] Quality control samples at 7.5, 150, and 750 ng/mL were assayed in duplicate with each batch of clinical samples. Between-run accuracy and precision were better than 10% throughout the range. The lower limit of quantification for the assay was 12 ng/mL.

Wheal-and-flare circumferences were traced with a pen at 10 minutes and transferred to paper by using transparent tape. The tracings were scanned, and the areas were calculated with SigmaScan (Jandel Scientific, San Rafael, Calif). By using this system, with wheal-and-flare sizes ranging from 0.05 to 5.0 cm^2 and a sample size of 14 children, differences of 20% could be detected with a 95% level of confidence.

Data analysis

Pharmacokinetics. The pharmacokinetic parameters were calculated by using the noncompartmental analysis approach. The elimination rate constant (Ke) was calculated from the plasma levocetirizine concentration (C) versus time (t) data measured after C_{max} had occurred, within 0.5 to 2 hours after dosing, by using equation 1:

$$C = C^{\circ}e^{-Ket}$$

where C° is the plasma concentration extrapolated to zero time after application of equation 1 by using WIN-NONLIN (Scientific Consulting, Apex, NC). The elimination half-life (t1/2) was calculated by using equation 2:

$$t1/2 = \ln 2/Ke$$

Although levocetirizine appears to be well absorbed, there is no intravenous formulation, and therefore the absolute bioavailability (F) is unknown. Total body clearance (Cl) and apparent volume of distribution (Vd) were calculated as Cl/F and Vd/F, as shown in equation 3:

$$Cl/F = AUC/Dose$$

and equation 4:

$$Vd/F = \frac{Cl/F}{Ke}$$

where AUC is the area under the plasma levocetirizine concentration versus time curve from time zero to 28 hours.

Pharmacodynamics. The pharmacodynamic parameters maximum effect attributable to medication (E_{max}) and plasma concentration producing 50% of E_{max} (EC_{50}) were calculated by using WIN-NONLIN (Scientific Consulting) and equation 5:

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