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:

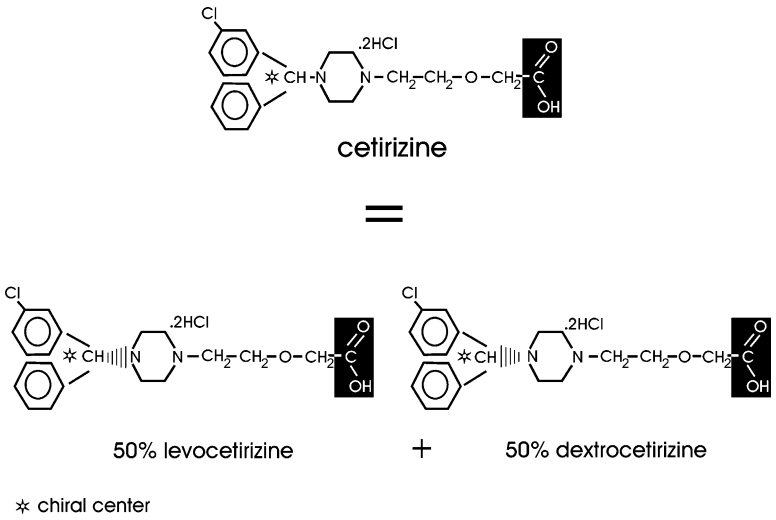

FIG 1. Structure of levocetirizine. The *asterisk* indicates the position of the chiral center. The molecular weight is 461.8 g/mole. The formula is $C_{21}H_{25}ClN_2O_3.2HCl$.

$$E = \frac{E_{max}\, C}{EC_{50} + C}$$

where E is the clinical effect, percentage suppression of histamine-induced wheal or flare, and C is the levocetirizine plasma concentration at which E occurs.[30]

Statistical analysis. Absolute wheal-and-flare areas over time were analyzed by using 1-way ANOVA, with subject and time as variates, analysis of covariance with predose wheal-or-flare areas as the covariates, and the Tukey and Bonferroni multiple-range tests. Differences were considered to be significant at P values of less than or equal to .05.

TABLE I. Demographics

N = 14* (9 boys)
Age: 8.6 ± 0.4 y
Weight: 30.4 ± 2.2 kg
Height: 132.5 ± 3.3 cm
Body mass index: 16.9 ± 0.6
Levocetirizine dose: 0.18 ± 0.01 mg/kg

All values are presented as means ± SEM.
*At the time of the study, 4 children were using an intranasal glucocorticoid for mild persistent allergic rhinitis, and 2 were using an orally inhaled glucocorticoid for mild persistent asthma.

RESULTS

The 14 Caucasian children (9 boys) with mild allergic rhinitis enrolled in the study had a mean (± SEM) age of 8.6 ± 0.4 years, a mean weight of 30.4 ± 2.2 kg, a mean height of 132.5 ± 3.3 cm, and a mean body mass index of 16.9 ± 0.6. They received a single 5-mg levocetirizine dose, which was equivalent to a mean dose of 0.18 ± 0.01 mg/kg (Table I). Complete pharmacokinetic data were available on only 13 of the 14 children because of missing blood samples in 1 child. The mean plasma levocetirizine concentration versus time plot is shown in Fig 2. The pharmacokinetic parameters, including elimination rate constants, area under the plasma concentration versus time curve, oral clearance, and apparent volume of distribution, were calculated by using noncompartmental analysis.

The mean maximum plasma levocetirizine concentration of 450 ± 37 ng/mL occurred at a mean time of 1.2 ± 0.2 hours (Table II). The mean terminal elimination half-life was 5.7 ± 0.2 hours, the mean area under the plasma levocetirizine concentration versus time plot was 3549 ± 342 ng/mL/h, the mean oral clearance rate was 0.82 ± 0.05 mL/min/kg, and the mean apparent volume of distribution was 0.4 ± 0.02 L/kg. The mean residence time was 6.8 ± 0.3 hours.

Pharmacodynamic data were available on all 14 children. Wheal-and-flare areas after testing with histamine phosphate, 1 mg/mL, are shown in Fig 3. Compared with predose values, the wheals were significantly suppressed ($P < .05$) from 1 to 28 hours, inclusive, with the mean maximum suppression of 97% ± 1% occurring from 2 to 10 hours. Compared with predose values, the flares were significantly suppressed ($P < .05$) from 1 to 28 hours, inclusive, with the mean maximum suppression of 93% ± 1% occurring from 2 to 24 hours. The relationships between the plasma levocetirizine concentrations and percentage suppression of wheal-and-flare responses compared with predose values versus time are shown in Fig 4.

Pharmacodynamic analysis resulted in calculation of an EC_{50} estimate of 16.1 ± 2.2 ng/mL and an E_{max} estimate of 104.3% ± 2.6% for wheal suppression, and an EC_{50} of 1.4 ± 0.1 ng/mL and an E_{max} of 94.5% ± 0.4% for flare suppression.

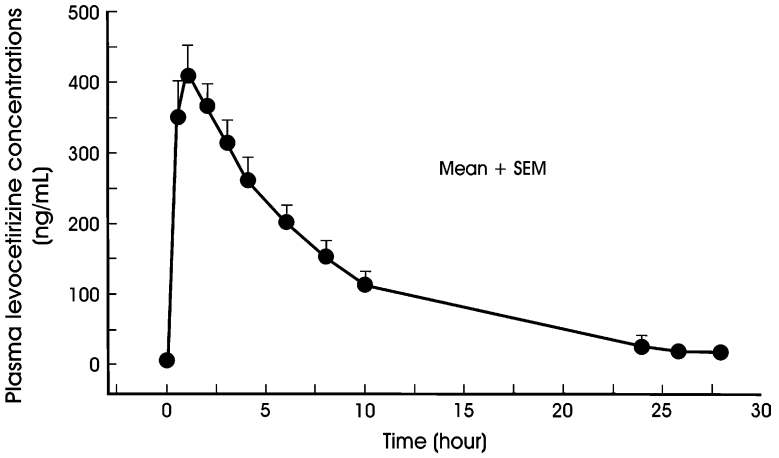

FIG 2. Plasma levocetirizine concentration (mean + SEM) versus time plot after ingestion of levocetirizine, 5 mg.

TABLE II. Levocetirizine pharmacokinetics

C_{max} (ng/mL)	450 ± 37
t_{max} (h)	1.2 ± 0.2
t1/2 (h)	5.7 ± 0.2
AUC (ng/mL/h)	3549 ± 342
Cl/F (mL/min/kg)	0.82 ± 0.05
Vd/F (L/kg)	0.4 ± 0.02

Values are presented as means ± SEM.
C_{max}, Maximum plasma concentration; t_{max}, time of maximum plasma concentration; *t1/2*, terminal elimination half-life; *AUC*, area under the plasma concentration versus time plot; *Cl*, oral clearance; *F*, oral bioavailability; *Vd*, apparent volume of distribution.

There were no serious adverse effects. Two children experienced some sneezing, nasal congestion, and discharge, and 1 child had intermittent coughing. The nasal symptoms were attributed to allergic rhinitis, and the cough was attributed to asthma; that is, the respiratory symptoms were considered to be due to underlying allergic diseases and to be unrelated to administration of the study drug. Two hours after dosing, one child had nausea that was relieved by eating, and 23 hours after dosing, another child had a sore stomach that was relieved by eating. These gastrointestinal symptoms were attributed either to overnight fasting or to anxiety about test procedures and were considered to be probably unrelated to the study drug. One child was more tired than usual 6 hours after the dose of the study drug, and 2 children were more tired than usual 12 hours after dosing. Although this fatigue might have been due to the intensity of the procedures during the first 12 to 13 hours of the study, it was considered to be possibly related to the study drug.

DISCUSSION

In this study levocetirizine appeared to be well absorbed, with peak plasma concentrations occurring at about 1 hour. In the absence of an intravenous levocetirizine formulation, true bioavailability cannot be determined. On the basis of the mean levocetirizine terminal elimination half-life of 5.7 hours that was found, dosing every 24 hours on a regular basis would be expected to lead to minimal or no levocetirizine accumulation in plasma. On the basis of significant wheal-and-flare suppression from 1 to 28 hours after dosing, levocetirizine would be expected to have significant H_1-antihistaminic activity throughout the dosing interval.

In pharmacokinetic and pharmacodynamic studies of H_1-antihistamines, although outcome measures such as blood tests and skin tests are highly objective, they are inherently invasive, and the studies therefore present unique challenges in children.[2,4] Study designs do not usually involve a placebo control,[7-20] not only because of ethical constraints and parental concerns about the use of placebo, but also because a potent H_1-antihistamine suppresses wheals and flares by up to 100%,[5,6,12,13] thus making it difficult to maintain double-masked observations and measurements.

The objective, standardized, histamine-induced wheal-and-flare bioassay is useful for studying the onset, amount, and duration of activity of H_1-antihistamines. Skin tests with histamine relate to the suppression of wheals, a primary symptom and sign in urticaria, and flares, which are caused by an axon reflex and are thus related to histamine indirectly rather than directly. Whether skin test suppression correlates with events in the airways remains controversial[31]; however, it is noteworthy that in allergy practice worldwide, skin tests with allergen are performed in lieu of nasal and bronchial allergen challenges to ascertain the relevance of allergens to allergic rhinitis and asthma symptoms, and in the clinical setting cutaneous responses are assumed to reflect airways responses.

The pharmacokinetics and pharmacodynamics of levocetirizine, reported here in children aged 6 to 11 years, differ slightly from those reported previously in adults with a mean age of 35 ± 2 years and a mean weight of

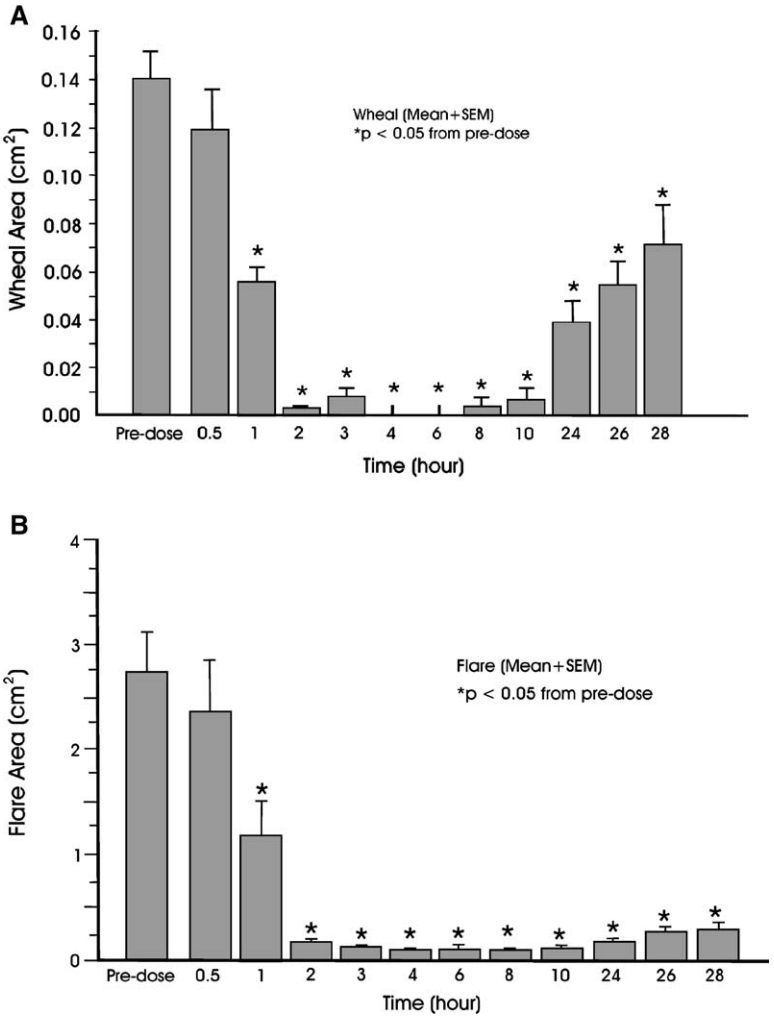

FIG 3. The effect of levocetirizine, 5 mg, on the wheals and flares produced by epicutaneous tests with histamine phosphate, 1 mg/mL. **A**, The wheals (+ SEM) were suppressed from 1 to 28 hours, inclusive ($P \leq .05$). **B**, The flares (+ SEM) were suppressed from 1 to 28 hours, inclusive ($P \leq .05$).

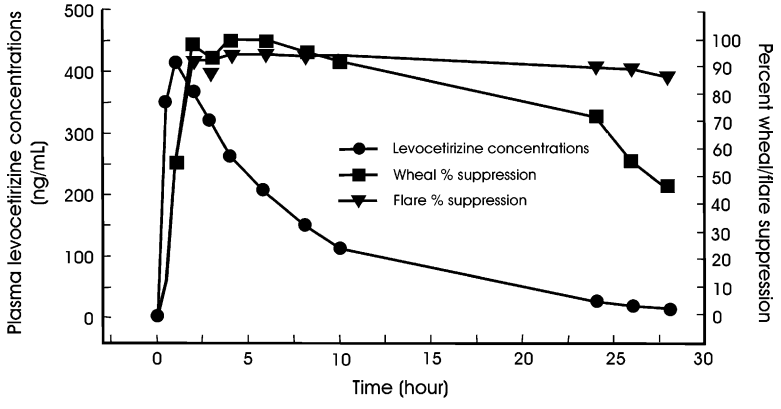

FIG 4. Mean plasma levocetirizine concentrations and mean wheal-and-flare percentage suppression compared with predose values, plotted versus time.

67.3 ± 2.3 kg, in whom the time of maximum plasma concentration is 0.73 ± 0.7 hours, the terminal elimination half-life value is 7.8 ± 0.3 hours, the clearance rate is 0.62 ± 0.02 mL/min/kg, and the apparent volume of distribution is 0.41 ± 0.02 L/kg.[24,25] As noted previously, after administration of radioactively labeled levocetirizine to adults, 85.4% of the drug is eliminated unchanged in the urine, and 12.9% is eliminated unchanged in the feces within 1 week.[26] The duration of action of a single levocetirizine dose is greater than 24 hours in adults.[27]

The pharmacokinetics and pharmacodynamics of levocetirizine reported here in children aged 6 to 11 years also differ from those reported previously in very young children. In a prospective study in children with a mean age of 20.7 ± 3.7 months and a mean weight of 11.6 ± 1.8 kg, the time of maximum plasma concentration was 1 hour, the terminal elimination half-life was 4.1 ± 0.67 hours, the clearance was 1.05 ± 0.10 mL/min/kg, and the apparent volume of distribution was 0.37 ± 0.06 L/kg.[20] Rapid elimination of levocetirizine was also found in a population pharmacokinetic study in which cetirizine was given to 343 children aged 14 to 46 months, and timed sparse blood samples were obtained at steady state for measurement of plasma levocetirizine (the active enantiomer or eutomer) and dextrocetirizine (the inactive enantiomer or distomer) values.[22,23] The population pharmacokinetic model used predicted that with increasing body weight, levocetirizine oral clearance would increase by 0.044 L/h/kg, and levocetirizine volume of distribution would increase by 0.639 L/kg. Taken together, the results of these 2 studies indicate that in very young children, compared with older children and adults, higher levocetirizine doses may be needed on a milligram per kilogram basis, and twice-daily dosing may be required.

Development of organ function and many of the maturational changes affecting pharmacokinetic disposition of drugs is ongoing throughout infancy and childhood, but elimination through the renal route is largely completed by age 4 to 5 years.[1] This study provides a rationale for administration of levocetirizine, 5 mg, once daily in children aged 6 to 11 years, as in adults, with the expectation of prompt onset of action and significant long-lasting antihistaminic activity at the H_1-receptor.

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