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Pharmacokinetics and Safety of Montelukast in Children Aged 3 to 6 Months

Barbara Knorr, MD, Lata Maganti, PhD, Rohini Ramakrishnan, PhD, Carol A. Tozzi, PhD, Elizabeth Migoya, PharmD, and Gregory Kearns, PharmD, PhD, FCP

The single-dose population estimate of the area under the concentration-time curve (AUC_{pop}) from time zero to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), and time to C_{max} (t_{max}) of montelukast 4-mg oral granules were investigated in infants aged 3 to 6 months. Montelukast concentrations were quantitated after a single 4-mg dose of montelukast oral granules. Pharmacokinetic parameters were determined using a population-based approach with a nonlinear mixed-effect, 1-compartment model with first-order absorption and elimination. Ninety-five percent confidence intervals for the AUC_{pop} ratio (3 to 6 months/6 to 24 months) were determined. Safety and tolerability

were assessed. Montelukast 4-mg oral granules in children 3 to 6 months of age yielded systemic exposure ($AUC_{pop} = 3644.3 \pm 481.5$ ng·h/mL) similar to that observed in children aged 6 to 24 months (3226.6 ± 250.0 ng·h/mL). Systemic exposure after a 4-mg dose of montelukast as oral granules is similar in children aged 3 to 6 months and 6 to 24 months.

Keywords: Bronchiolitis; population pharmacokinetics; controlled clinical trial; pediatrics

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Viral-induced bronchiolitis is the most common respiratory disease in children younger than 2 years of age, with respiratory syncytial virus (RSV) being the most common causal agent.¹ Viral-induced bronchiolitis may lead to episodes of respiratory symptoms (eg, cough, wheezing) lasting weeks after the initial infection. Moreover, severe infection with RSV may itself be a risk factor for development of asthma in later life.² Current therapies are largely supportive and of modest benefit in the treatment

of postbronchiolitic respiratory symptoms. Recent studies suggest that cysteinyl leukotrienes (CysLTs) may play a role in the pathobiology of the respiratory symptoms subsequent to viral-induced bronchiolitis.^{3,4} Therefore, it is possible that CysLT-blocking agents may be beneficial in the treatment of these respiratory symptoms.

Montelukast, a potent orally active CysLT₁ receptor antagonist, has demonstrated efficacy in the treatment of asthma symptoms in adults⁵ and children,^{6,7} in attenuating exercise-induced bronchoconstriction in adults⁸ and children,⁹ and in relieving symptoms of seasonal allergic rhinitis.¹⁰⁻¹³ In addition, recently published results from a randomized, placebo-controlled study in children aged 3 to 36 months hospitalized with RSV-induced bronchiolitis demonstrated treatment with montelukast (5-mg crushed chewable tablet), compared with placebo, was associated with significant improvement in the respiratory symptoms subsequent to RSV-induced bronchiolitis, suggesting that montelukast may provide benefit in this disease.¹⁴

Given viral-induced bronchiolitis affects very young children, including those under 6 months of age, and based on the potential role of CysLTs in the

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pathophysiology of this disorder, there may be a putative role for montelukast in its treatment.¹⁴ It is therefore important that the pharmacokinetic properties and safety of montelukast be evaluated in this population. Thus, the purpose of this study was to evaluate both the pharmacokinetics of montelukast after a single, 4-mg oral dose and the apparent safety of 2 multiple-dose regimens (4 mg and 8 mg) in infants with active bronchiolitis or a history of bronchiolitis and respiratory symptoms. The effect of age on montelukast disposition was examined by comparison of the pharmacokinetic parameters with results obtained from a prior study (using identical doses and experimental approaches) conducted in older infants and children ranging in age from 6 to 24 months.

METHODS

Patients

Enrolled patients were boys or girls 3 to 6 months of age with active bronchiolitis or having a history of bronchiolitis and currently experiencing asthma-like symptoms. Patients weighed between 4.8 kg and 8.5 kg and were within the 5th to 95th percentile of height for weight. Patients had to be receiving semi-solid food for at least a week and have been fed applesauce or apple-containing products at least twice before the administration of montelukast. Patients were excluded if they had surgery within 8 weeks of the study or had any clinically significant disease or condition other than bronchiolitis or asthma-like symptoms. Patients were also excluded if they had taken astemizole within 3 months; terfenadine, loratadine or any theophylline preparation within 10 days of visit 1; or oral β -agonists within 24 hours of the first montelukast dose.

The study protocol was approved by the ethical committees of the respective clinical institutions that participated in the investigation at 3 sites: Chile (San Borja Arriaran Hospital), Columbia (Fundación Santa Fe de Bogotá), and Peru (Instituto Especializado de Salud del Niño), South America. Before the initiation of any study-related procedure, written informed consent was obtained from parents or guardians of all patients.

Study Design

This was a multicenter, randomized, 3-period, 14-day study evaluating the multiple-dose safety of the 4-mg

and 8-mg oral granules doses of montelukast and the population pharmacokinetics of montelukast after administration of a single oral 4-mg dose of oral granules in patients aged 3 to 6 months. During all 3 periods, study drug was administered as 2 packets (packet A [montelukast or placebo] and packet B [montelukast or placebo]) of the oral granules formulation. Packets were administered sequentially on a tablespoonful (approximately 15 gm) of applesauce.

Patients were evaluated for study inclusion at a prestudy visit (visit 1) 3 to 7 days before the beginning of the study, at which time a physical examination was performed, vital signs were obtained, and blood samples were collected for safety evaluations and pretreatment montelukast plasma concentration assays.

Period 1 (study day 1) was a single-blind, 1-day pharmacokinetic period in which all patients received a single witnessed dose of 4-mg montelukast oral granules. During period 1, patients were randomly assigned to 1 of 2 possible sparse plasma sampling schedules: A ($n = 9$; samples at predose and 2.5, 6, and 10 hours postdose) and B ($n = 5$; samples at predose and 2, 4, and 24 hours postdose).

Period 2 (study days 2 through 7) was a double-blind, placebo-controlled, 6-day treatment period designed to assess safety in which all patients received either montelukast 4-mg oral granules or matching-image oral granules placebo administered once daily in the morning. Period 2 began with a witnessed dose of study medication in the clinic after the 24-hour plasma sample for period 1 was obtained. Caregivers administered blinded study drug for the following 5 days at the same time each morning and completed a daily medication diary card recording dosing times and drug consumption.

Period 3 (study days 8 through 14) was a double-blind, placebo-controlled, 7-day safety period in which all patients received either montelukast 8-mg oral granules or matching-image oral granules placebo administered once daily in the morning. Patients returned to the study center on day 8 to begin period 3, in which they received a witnessed dose of study medication in the clinic and then were discharged from the study center. Caregivers administered blinded study drug for the following 5 days at the same time each morning and completed a daily medication diary card recording dosing times and drug consumption. On study day 14, patients returned to the study center, where they received a final, witnessed dose of study drug and were then discharged to home.

During all 3 study periods, patients were allowed to have treatment with inhaled or nebulized

albuterol or salbutamol, inhaled or nebulized cromolyn, and inhaled or nebulized, oral, or parenteral corticosteroids for the treatment of viral-induced bronchiolitis and worsening asthma-like symptoms. Use of oral β -agonists was also permitted once the pharmacokinetic sampling in period 1 had been completed.

Dose Selection

Initial dose selection was based on the assumption that systemic montelukast exposure associated with beneficial effects in treatment of asthma in children would represent a reasonable target exposure for infants with respiratory symptoms (eg, cough, wheeze) associated with viral-induced bronchiolitis. Because the goal of therapy with montelukast in the treatment of viral-induced bronchiolitis would be to treat underlying inflammation-associated respiratory symptoms, it is reasonable to extrapolate that the clinically effective dose of montelukast in asthma in this age group (4-mg oral granules) would be efficacious in the treatment of the respiratory symptoms subsequent to viral-induced bronchiolitis. As well, previous studies suggested a favorable safety profile for the 4-mg oral granules dose in children aged 6 to 24 months with asthma^{15,16} and for a crushed 5-mg tablet in children aged 3 to 36 months with bronchiolitis.¹⁴ Given the wide therapeutic index of montelukast and prior experience with the drug in pediatric populations,^{6,15} it was anticipated that both the 4-mg and 8-mg doses would be well tolerated in patients aged 3 to 6 months.

Because planned efficacy studies of montelukast included a dose-ranging study, 2 doses (ie, 4 mg and 8 mg) of the drug administered as oral granules were initially evaluated in patients aged 3 to 6 months before initiating larger efficacy studies in this pediatric subpopulation. To facilitate comparison of the pharmacokinetic data to those previously obtained in patients 6 to 24 months of age,¹⁷ the 4-mg dose of montelukast granules was selected for pharmacokinetic evaluation in the current study.

Montelukast Assay

At each sampling time according to the schedules described above, 3-mL blood samples were drawn into evacuated blood collection tubes containing sodium heparin as the anticoagulant. Blood was centrifuged immediately, and the plasma fraction (≥ 1.5 mL) was transferred to opaque cryotubes that were

protected from light and stored at -70°C until shipment for assay. Plasma concentrations were determined by a high-pressure liquid chromatography (HPLC) assay method. The assay procedure was found to be selective for montelukast, and no detectable interferences at the retention times for the analyte or internal standard were found in plasma double blank samples. Briefly, a 300- μL plasma sample was prepared for analysis by the addition of an internal standard, followed by protein precipitation with 400 μL of acetonitrile. The sample was vortexed for 30 seconds and then injected into an Agilent 1100 system (Agilent Technologies, Palo Alto, Calif) for HPLC analysis. Montelukast and the internal standard were separated through an Apex octadecyl column (4.6×50 mm, 3 μm) using a mobile phase of acetonitrile/ammonium phosphate (0.05 M, pH 3.5; 61:39 volume/volume) and detected via a Shimadzu fluorescence detector (Shimadzu Corp, Kyoto, Japan) at excitation/emission wavelengths of 350/400 nm. Retention times were 3.2 minutes for montelukast and 4.0 minutes for internal standard. The dicyclohexylamine (DCHA) salt form of montelukast was used as the standard; all results were reported as nanograms of free montelukast per milliliter of plasma.

The lower limit of quantitation for this assay was 3 ng/mL, with a linear calibration range of 3.0 to 964 ng/mL for montelukast. Two sets of low (4.8 ng/mL), middle (48.2 ng/mL), and high (482 ng/mL) quality control samples were assayed together with study samples in an assay run. The assay accuracy obtained in the quality control samples ranged from 104.9% to 105.8% of the nominal values for montelukast. Assay precision in the quality control samples ranged from 0.31% to 0.84% coefficient of variation. All assays were performed at the Merck Research Laboratories Drug Metabolism Department (West Point, Pa).

Pharmacokinetics and Statistical Methods

A population pharmacokinetic approach using a nonlinear, mixed-effect, 1-compartment model with first-order absorption, and elimination was fitted to the available montelukast plasma concentration-time data. The pharmacokinetic model and validation thereof have been described elsewhere.¹⁸ This approach was based on the assumption that montelukast would exhibit linear pharmacokinetic properties in this age range, similar to those previously observed in older children and adults.^{19,20} An identical population pharmacokinetic approach was used for the previous study in patients aged 6 to 24

months,¹⁷ who served as the historical control group for the purpose of comparison of pharmacokinetic parameters in the current study to assess possible age dependence in montelukast disposition across the 3- to 24-month age range. In addition, the data from patients aged 3 to 6 months were pooled with the historical data from 6- to 24-month-old patients, and pharmacokinetic parameter estimates were calculated for 3- to 24-month-old patients.

The following pharmacokinetic parameter estimates were obtained after administration of a single 4-mg dose of montelukast oral granules: population area under the concentration-time curve (AUC_{pop}), clearance/bioavailability (CL/F), maximum observed concentration (C_{max}), time of C_{max} (t_{max}), and apparent elimination half-life ($t_{1/2}$). Population AUC was the primary parameter used for relative comparison of montelukast dose-exposure between the 3- to 6-month-old age group and the 6- to 24-month-old historical controls¹⁷ and also in the calculation of the ratios for comparison between the groups. Ratios were determined using 2 age-related subsets from the historical control group (ie, 6- to 12-month-olds and 6- to 24-month-olds). Ninety-five percent (95%) confidence intervals (CIs) for the AUC_{pop} ratios (3 to 6 months/children 6 to 24 months [historical data] and 3 to 6 months/children 6 to 12 months [historical data]) were calculated. Data from patients aged 3 to 6 months were pooled with the historical data from patients aged 6 to 24 months,¹⁷ and population estimates for pharmacokinetic parameters (AUC_{pop} , CL/F , C_{max} , t_{max} , and apparent $t_{1/2}$) for patients 3 to 24 months old also were calculated.

The individual pharmacokinetic parameter estimates (AUC from time zero to infinity [$AUC_{0-\infty}$], C_{max} , CL/F , t_{max} , and apparent $t_{1/2}$) obtained from the population modeling described above were used to conduct formal statistical comparisons between the 2 age groups (3- to 6-month-olds vs 6- to 24-month-olds). These comparisons were made by comparing appropriately transformed parameter estimates (eg, $AUC_{0-\infty}$, C_{max} , and CL/F were log transformed; t_{max} was rank transformed and apparent $t_{1/2}$ was transformed by taking its reciprocal) using a 2-tailed, Student *t* test with the significance limit set at $\alpha = .05$.

To further explore the association between development and montelukast disposition, both $AUC_{0-\infty}$ and apparent elimination $t_{1/2}$ were examined as a function of age for patients over a range of 3 to 24 months. Pearson correlation coefficients and corresponding statistics were generated from linear and nonlinear (where appropriate) regressions between age and the pharmacokinetic parameters.

Table I Patient Demographics and Baseline Characteristics

Total number of patients	14
Age, median (range), mo	4 (3-5)
Age, n	
3 months	6
4 months	2
5 months	6
Gender, n (%)	
Boys	9 (64)
Girls	5 (36)
Race, n (%)	
Hispanic	14 (100)
Weight, mean (range), kg	6.8 (4.8-8.5)
Height mean (range), cm	61.9 (56-66)

Safety Evaluations

A physical examination was performed 3 to 7 days before administration of the study drug in period 1 and on study day 14 (period 3). Clinical laboratory tests (hematology and serum chemistry) were performed 3 to 7 days before administration of the study drug in period 1, on study day 8 (period 2), and on study day 14 (period 3). Vital sign measurements, including blood pressure, heart rate, respiratory rate, and oral or tympanic temperature, were evaluated 3 to 7 days before drug administration, 6 times during period 1, and both predose and post-dose on study days 8 and 14 of periods 2 and 3, respectively. Adverse experiences were recorded by the investigator, who determined the severity and causal relationship to study medication.

RESULTS

Patients

Demographic data for the 14 patients who participated in the study are contained in Table I. All 14 patients received a single 4-mg oral dose of montelukast granules during the pharmacokinetic study period (period 1). During the multiple-dose periods (periods 2 and 3), 9 patients received 4-mg and 8-mg daily doses of montelukast and 5 received placebo. To assess the percentage of study drug consumed by patients, study sites and caregivers documented the approximation of oral granules consumption on a worksheet (study sites) or diary card (caregivers). Overall, for the 14-day study, mean study drug consumption was 95.9%.

Table II Summary Statistics for AUC_{pop} of Montelukast After Administration of a Single 4-mg Dose of Oral Granules to Pediatric Patients

Population Age Group (mo)	n	AUC _{pop} (ng·h/mL) ^a	95% CI	Population Mean Ratio (95% CI) ^b
3 to 6	14	3644.3 ± 481.5	2534-4755	—
6 to 24	26 ^c	3226.6 ± 250.0	2709-3744	1.13 (0.83-1.55)
6 to 12	12 ^c	3470.9 ± 499.3	2341- 4600	1.05 (0.69-1.60)
3 to 24	42 ^d	3629.2 ± 243.1	3136-4122	—

AUC_{pop}, area under the concentration-time curve determined by population pharmacokinetic analysis; CI, confidence interval.

a. Values are ± standard error of the mean.

b. Population mean ratio = AUC_{pop} of 3 to 6 month olds/given population age group.

c. Historical control data.

d. Two patients not included in the original study because model would not converge¹⁷ were included in this analysis.

Table III Summary Statistics for Population Estimates of Pharmacokinetic Parameters for Montelukast After Administration of a Single 4-mg Dose of Montelukast Oral Granules to Pediatric Patients

Population Age Range (mo)	n	C _{max} (ng/mL) ^a	t _{max} (h) ^a	t _{1/2} (h) ^a	CL/F (mL/min) ^a
3 to 6	14	561.1 ± 78 (381-741)	2.1 ± 0.4 (1.1-3.1)	0.94 ± 0.38 (0.05-1.82)	18.3 ± 2.4 (12.7-23.9)
6 to 24	26 ^b	514.4 ± 43 (425-604)	2.2 ± 0.1 (2.0-2.5)	1.23 ± 0.17 (0.89-1.57)	20.7 ± 1.6 (17.3-24.0)
6 to 12	12 ^b	583.5 ± 85 (392-775)	2.1 ± 0.3 (1.4-2.7)	1.04 ± 0.28 (0.42-1.67)	19.2 ± 2.8 (13.0-25.5)
3 to 24	42 ^c	582.3 ± 47 (486-678)	1.9 ± 0.3 (1.3-2.5)	0.75 ± 0.20 (0.34-1.17)	18.4 ± 1.2 (15.9-20.9)

C_{max}, maximum observed concentration; t_{max}, time of C_{max}; t_{1/2}, half-life; CL/F, clearance/bioavailability.

a. Values are expressed as ± standard error of the mean; values in parentheses are 95% confidence intervals.

b. Historical control data.

c. Two patients not included in the analysis of the original study because model would not converge¹⁷ were included in this analysis.

Pharmacokinetics

Population AUC estimates with 95% CIs after administration of a single 4-mg dose of oral granules in patients aged 3 to 6 months, 6 to 12 months, 6 to 24 months,¹⁷ and 3 to 24 months (pooled data) are presented in Table II. The mean ratios for AUC_{pop} for patients 3 to 6 months of age were comparable to those for patients 6 to 24 months (ratio = 1.13) and 6 to 12 months of age (ratio = 1.05).

Table III contains summary data for other montelukast population pharmacokinetic parameters (C_{max}, t_{max}, apparent t_{1/2}, and CL/F) from the current study (patients aged 3 to 6 months), the previous investigation conducted in infants and children aged 6 to 24 months¹⁷ and 2 other populations created from the aforementioned data sets (ie, ages 6 to 12 months and 3 to 24 months). The values for AUC_{0-∞}, C_{max}, CL/F, t_{max}, and apparent t_{1/2} after a single 4-mg oral montelukast dose did not appear to differ

significantly among the age groups ($P > .800$). No statistically significant ($P > .400$) relationships or apparent trends were observed when AUC_{0-∞} (Figure 1) and apparent t_{1/2} estimates (Figure 2) were examined as a function of age (eg, Pearson correlation coefficient = $-.13$ and $.10$ for AUC_{0-∞} and apparent t_{1/2}, respectively).

Safety and Tolerability

Twenty-four clinical adverse experiences were reported in 8 patients, and 3 laboratory adverse experiences were reported in 3 patients. There were no serious adverse experiences, and no patient discontinued study participation because of a clinical or laboratory adverse experience. The most common clinical adverse experiences were asthma, diarrhea, and loose stools. Six adverse experiences were determined by the investigators to be possibly drug related (4 mg montelukast: diarrhea, loose stools,

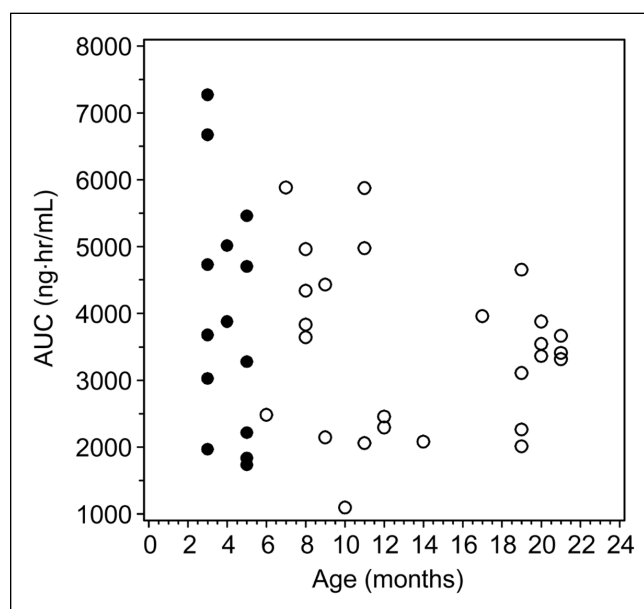


Figure 1. Individual area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) estimates of montelukast versus age in 3- to 24-month-old patients. ●, 3 to 6 months; ○, 6 to 24 months.

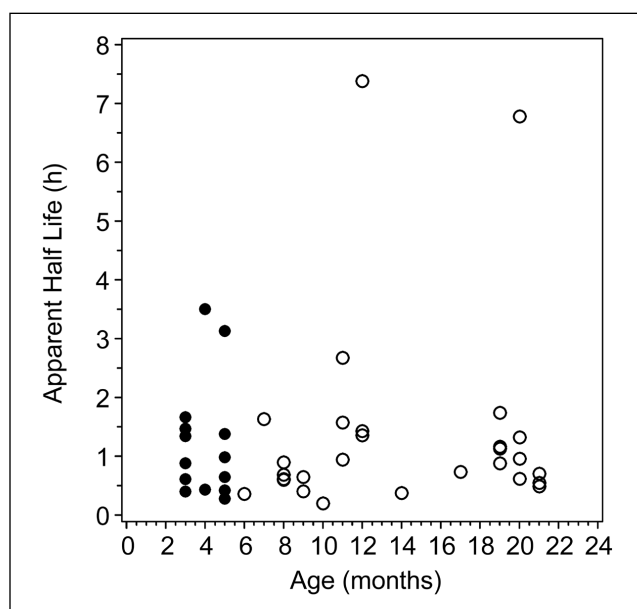


Figure 2. Individual apparent $t_{1/2}$ estimates of montelukast versus age in 3- to 24-month-old patients. ●, 3 to 6 months; ○, 6 to 24 months.

nausea; 8 mg montelukast: diarrhea, loose stools; placebo: diarrhea). The 3 reported laboratory adverse experiences were anemia (8 mg montelukast [2 patients]; placebo [1 patient]), none of which was considered serious or drug related.

DISCUSSION

Viral-induced bronchiolitis, particularly RSV-induced bronchiolitis, frequently occurs in infants.²¹ The symptoms of this disease are largely the result of airway inflammation, thereby producing a plausible, mechanism-based role for montelukast treatment. The young age of the patient population afflicted with viral-induced bronchiolitis provided the rationale for the current pharmacokinetic study in children aged 3 to 6 months as a necessary antecedent for possible future investigations of its safety and efficacy in this subpopulation.

This study demonstrated that multiple doses of 4 mg montelukast, followed by 8-mg doses, given over 14 days were generally well tolerated in infants. Similar to montelukast dose-ranging studies (ie, 2 to 200 mg) in adults,²⁰ no apparent dose-related adverse experiences were identified in this study. Adverse experiences determined by the investigator to be

related to study therapy occurred at both doses of montelukast and in the placebo group. Moreover, the safety profile observed in this age group was similar to that observed in older children^{7,17,19} and adults.⁵

Very young children have limited blood volumes, and collection of blood samples to support classical pharmacokinetic analyses in the youngest patients often presents a technical and logistical challenge. To address this challenge, a sparse sampling scheme (ie, 2 sampling schedules with 1 predose and 3 postdose samples), followed by use of a population pharmacokinetic analysis approach, was used, as was done in a previous study in patients 6 to 24 months of age.¹⁷ This approach enabled accurate estimation of patient-specific pharmacokinetic parameters sufficient to explore potential age effects on montelukast disposition.

Montelukast is metabolized in the liver by the cytochrome P450 enzyme system (CYP) and specifically, by CYP3A4 and CYP2C9 isoforms.²² As previously reviewed,²³ pharmacokinetic data from studies using substrates of CYP3A4 and CYP2C9 suggest the potential for increased plasma clearance in young children and, consequently, the need for age-specific dosing schemes to produce an extent of systemic exposure likely to yield comparable drug efficacy and safety observed for adults. In contrast, data from

the present study and previous investigations of montelukast disposition^{17,24} do not apparently support marked developmental differences in the age range down to 3 months.

As illustrated by the data in Tables II and III, montelukast pharmacokinetics from our study cohort after a single 4-mg dose were similar to those obtained in previous pediatric studies¹⁷ that used an identical dose and approach to study. As well, our finding of no apparent association between age and montelukast pharmacokinetic parameters suggests that development does not produce marked differences in the disposition of this drug in infants and children between 3 and 24 months of age.

The implications of our pharmacokinetic data for young infants and those for young children up to 24 months of age reside with the apparent dose-exposure-response relationship for montelukast. For the beneficial effects of montelukast in asthma, a target exposure appears to range between 2569 and 3226.6 ng/h.mL (based on the mean geometric AUC) for both adults and children.¹⁷ Given the previously reported dose proportionality in montelukast pharmacokinetics²⁵ and the apparent similarity in both the dose-exposure profile (Table II) and the disposition of this drug in infants and young children (Table III), it would appear that a fixed dose of the drug may be sufficient for further evaluating the safety and efficacy of montelukast in young infants with postviral bronchiolitis.

In conclusion, the present study demonstrated that both a 4-mg and 8-mg oral granule dose of montelukast was well tolerated in patients aged 3 to 6 months. As well, the pharmacokinetics of the drug over this age range was similar to those in older infants and young children.

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