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Pharmacokinetics and Safety of Montelukast Oral Granules in Children 1 to 3 Months of Age With Bronchiolitis

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The single-dose pharmacokinetics of montelukast 4-mg oral granules and tolerability of daily administration of 2 different doses of montelukast (4 mg and 8 mg given once daily for 7 days) versus placebo were evaluated in 12 infants 1 to 3 months of age with bronchiolitis or a history of bronchiolitis and asthma-like symptoms. The population area under the concentration-time curve estimate after a single 4-mg dose of montelukast was $13\,195.7 \pm 2309.8$ (standard error) ng.hr/mL, 3.6 times higher than historical values in infants 3 to 24 months of age. Six patients had 10 total clinical adverse experiences; none was considered serious or drug related. Three patients had transient drug-related increases in aspartate aminotrans-

ferase (montelukast 8 mg [$n = 2$]; placebo [$n = 1$]). Despite increased systemic exposure after administration of a single dose of montelukast 4-mg oral granules in infants 1 to 3 months of age compared with that in pediatric patients 3 to 24 months of age, administration of montelukast at 4 and 8 mg once daily for 7 days in 1- to 3-month-old infants was generally well tolerated.

Keywords: Montelukast; infants; bronchiolitis; pharmacokinetics; safety

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In infants, bronchiolitis is a common lower respiratory tract condition frequently associated with infection caused by viral pathogens that can include parainfluenza, influenza, and, most commonly, respiratory syncytial virus (RSV).¹⁻³ Respiratory syncytial virus bronchiolitis is a major cause of all hospitalizations of infants younger than 1 year, with infants younger than 6 months accounting for the highest rates of hospitalization for this condition in

the United States, and the greatest incidence occurring in infants at 2 months of age.⁴⁻⁶

During the acute phase of infection, inflammation of the tracheobronchial tract produces respiratory distress and wheezing; the latter symptom can persist for up to a year.⁷ While it is unclear whether severe viral infections in infancy increase the risk of recurrent wheezing later in life or whether bronchiolitis is an early sign of an underlying predisposition to wheezing, several studies have shown that infants hospitalized for severe bronchiolitis are more likely to have respiratory diseases as older children^{1,7-11} and as adults.¹¹⁻¹³ Recent evidence suggests a role for cysteinyl leukotrienes (CysLT₁) in the development of persistent respiratory symptoms after viral bronchiolitis.¹⁴⁻¹⁷ Accordingly, the clinical pharmacology of montelukast has been explored in both infants and young children.¹⁸

Following oral administration, montelukast is absorbed well.¹⁸ The mean oral bioavailability of montelukast

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(4-mg oral granules) is approximately 70%. It is more than 99.5% bound to plasma proteins, with average steady-state volume of distribution ($V_{d_{ss}}$) of 8 to 11 L in adults. In humans, montelukast undergoes extensive metabolism, with only a small fraction of the dose being excreted as the parent drug in bile. Available data suggest that montelukast metabolism involves both acyl glucuronidation and oxidation; in vitro data indicate that CYP2C9 and CYP3A4 are the P450 isoforms mediating the oxidative metabolism of montelukast.

Developmental changes in organ function, body composition, and the composition and amount of plasma proteins, such as albumin and α_1 -acid glycoprotein, can influence drug absorption, binding, distribution, and clearance.¹⁹ Age-dependent changes in the gastrointestinal tract, intraluminal pH, gastric emptying, intestinal motility, activity of intestinal drug-metabolizing enzymes, and efflux transporters may alter the rate and extent of the bioavailability of a drug in infants and children as compared with those for adults.

The expression and activity of drug-metabolizing enzymes (both phase I and II) can also change markedly during development.¹⁹ The activity of CYP3A4 and CYP2C9, the enzymes involved in the biotransformation of montelukast, are generally reduced in the first month of life and do not reach adult levels until 3 months of age or later.²⁰⁻²² Therefore, the pharmacokinetics of montelukast in infants 1 to 3 months of age may be different from older children and adults due to these developmental changes.

Data from 116 infants aged 3 to 36 months who were hospitalized with RSV bronchiolitis and randomized to receive montelukast 5 mg or placebo showed that montelukast improved the number of respiratory symptom-free days and reduced daytime cough compared with placebo.²³ In children aged 6 to 24 months with asthma, montelukast given as 4-mg oral granules was generally well tolerated and provided a systemic exposure similar to that of the 10-mg film-coated tablet that is clinically effective in adults for asthma and allergic rhinitis.²⁴ In infants 3 to 6 months of age, montelukast 4 and 8 mg given as oral granules was well tolerated, and the pharmacokinetic profile was similar to that observed in children 6 to 24 months of age.²⁵ Given the potential for therapeutic utility of montelukast in young infants with bronchiolitis, we undertook an evaluation of the pharmacokinetics and tolerability of the oral granule formulation of the drug in patients 1 to 3 months of age.

METHODS

Study Design

This was a randomized, 3-period, multiple-dose, multicenter study, conducted from December 1, 2004, through October 31, 2005, at 4 centers in the United States, Colombia, and Chile. At the start of the study, 12 infants aged 1 to 3 months were randomized to 1 of 2 treatment schedules: a single dose of montelukast 4-mg oral granules in period 1; montelukast 4 mg once daily for 6 days in period 2; and montelukast 8 mg once daily for 7 days in period 3 (group A) or a single dose of montelukast 4-mg oral granules in period 1, and matching-image placebo once daily in periods 2 and 3 (group B). The random allocation schedule with a blocking factor of 6 was generated by a statistician at Merck & Co Inc (Rahway, New Jersey). Study drug was supplied in packets containing oral granules of either montelukast 4 mg or matching-image placebo.

Patients

Infants aged 1 to 3 months were eligible to enroll in the study if they had either active bronchiolitis or a history of bronchiolitis with current asthma-like symptoms and were otherwise in good health. They had to be in the 5th to 95th percentiles of height and weight for their age and have a minimum total body weight of 3.5 kg. They must have been fed infant formula at least twice in their lifetime before study drug administration to ensure the infants were tolerant to the formula before it was used to deliver study drug.

Exclusion criteria included any clinically significant disease or condition other than bronchiolitis or asthma-like symptoms; gestational age at birth less than 36 weeks; administration of oral β -agonists within 24 hours preceding the first dose of montelukast; administration of macrolide antibiotics, azole antifungals, rifampin, theophylline preparations, terfenadine, or loratadine within 10 days before study entry; administration of astemizole any time before study entry; allergy to infant formula; anemia or intravascular volume status that would preclude blood sampling for pharmacokinetic analyses; and surgery within 4 weeks before study entry. Patients were evaluated 3 to 7 days before the first dose of study drug for inclusion in the study by way of medical history, assessment of vital signs, physical examination, and laboratory tests, including serum electrolytes, glucose, total protein, hepatic transaminases, total bilirubin, blood urea nitrogen

(BUN), serum creatinine, and complete blood count with differential.

The study protocol was approved by the ethical committees of the institutions that participated in the study (Ethics Scientific Committee, Metropolitan Central Health Service for Hospital Clinico San Borja-Arriaran; Ethics Scientific Committee, Valdivia Health Service for Hospital Base Valdivia; Research Ethical Committee of Hospital Fundacion Santa Fe de Bogotá for Hospital Fundacion Santa Fe de Bogotá; and the Children's Mercy Hospital IRB for Children's Mercy Hospitals and Clinics). Written informed consent was obtained from parents or guardians of all patients prior to the conduct of any study procedure.

Procedures

Period 1 was an open-label, 1-day (study day 1) evaluation designed to assess the pharmacokinetics of a single 4-mg dose of montelukast. On day 1, each infant received 1 packet of montelukast 4-mg oral granules mixed with 5 mL of infant formula as an observed dose at the study center prior to pharmacokinetic sampling. The entire dose was successfully administered to each child. Previous studies indicate there is minimal food effect on montelukast pharmacokinetics.²⁶

After administration of the study drug, study participants were randomized to 1 of 2 sparse blood-sampling schedules: 2.5, 6, and 10 hours or 2, 4, and 24 hours after dosing. Vital signs (blood pressure, pulse, respiratory rate, and temperature) were evaluated immediately before dosing and 1, 2, 4, 6, and 24 hours after dosing.

Period 2 was a 6-day (study days 2-7), double-blind, placebo-controlled, multiple-dose safety assessment of montelukast given once daily at 4 mg. Period 2 began after completion of the 24-hour procedures for period 1. Patients received either montelukast 4-mg oral granules or matching-image placebo according to their treatment group assignment. The first dose was witnessed at the study center, and the remaining doses were administered at home.

Period 3 was a 7-day (study days 8-14), double-blind, placebo-controlled, multiple-dose safety assessment of montelukast 8 mg. On the first day of period 3, vital signs were evaluated as described for period 1, and the first witnessed dose of study drug was administered at the study center; on days 9-13, doses were administered at home. Vital signs were evaluated on day 14 or at discontinuation, and the final dose was administered at the study center.

In periods 2 and 3, 2 packets of study drug (each containing either montelukast 4 mg or matching-image

placebo) were administered to each patient once daily (6 days in period 2 and 7 days in period 3) at 8 AM mixed with 5 mL of infant formula. Caregiver compliance with study drug administration was assessed from packet counts and diary cards.

Safety Analysis

Safety was monitored from study start through 14 days after last dose of study drug. Prestudy evaluations included physical examination, medical history, vital signs (blood pressure, pulse, respiratory rate, temperature), and laboratory safety tests (as described for inclusion criteria). Vital signs were evaluated before in-clinic administration of study drug, as described above, and laboratory safety tests were performed on the last day of period 3. Adverse experiences were reviewed with the study participant's caretaker at the predose evaluation of each study period and at the postdose visit on day 14 or at discontinuation. On outpatient days, adverse experiences were monitored by telephone calls to the caretakers halfway between clinic visits. All adverse experiences were evaluated by the study investigator for severity, seriousness, and possible association with study drug. Medications permitted throughout the study consisted of inhaled or nebulized albuterol, cromolyn, and parenteral or oral corticosteroids. Oral β -agonists were permitted in periods 2 and 3.

Montelukast Assay

Venous blood samples (1 mL each) were collected into sodium heparinized glass tubes at specified time points during period 1 for montelukast quantitation. Samples were centrifuged, and the plasma was removed by manual aspiration and transferred to NUNC CryoTube vials (Nunc A/S, Roskilde, Denmark), which were stored protected from light at -70°C until they were shipped on dry ice to Merck Research Laboratories (West Point, Pennsylvania) for quantification of montelukast by reverse-phase high-pressure liquid chromatography (HPLC). Under yellow light, samples were prepared for analysis by the addition of an internal standard (an analog of montelukast) and acetonitrile to precipitate the protein. The sample was mixed and centrifuged, and the supernatant was injected onto a PerkinElmer 200 Series HPLC system (PerkinElmer Life and Analytical Sciences Inc, Waltham, Massachusetts) using an Apex ODS 3 micron, 50 mm $\times$ 4.6 mm, column (Jones Chromatography, Lakewood, Colorado)

with a mobile phase of 61% acetonitrile and 39% ammonium phosphate buffer 50 mM (pH 3.5) at a flow rate of 2.0 mL/min.

Detection was accomplished with a Shimadzu RF-10AXL fluorescence detector (Shimadzu Scientific Instruments, Columbia, Maryland) with excitation/emission wavelengths at 350 nm/400 nm. The lower limit of quantitation was 3 ng/mL, and the assay was linear from 3 to 1000 ng/mL. Low, middle, and high-quality control samples of montelukast (8.0, 400, and 800 ng/mL) were analyzed with study samples in each assay run. For the quality control samples, the interday precision ranged from 0.49 to 1.74 percent coefficient of variation (%CV), and the interday accuracy ranged from 100% to 103.7%.

Pharmacokinetics

The pharmacokinetic parameter estimates (population estimates for area under the concentration-time curve [AUC_{pop}], clearance after oral administration [Cl/F , where F = oral bioavailability], maximum plasma concentration [C_{max}], time to C_{max} [T_{max}], and apparent elimination half-life [$t_{1/2}$]) after administration of a single 4-mg dose of the montelukast oral granules on study day 1 (period 1) were determined for the 1- to 3-month-old participants in the current study ($N = 12$). The results were compared with those determined in infants 3 to 24 months of age from prior investigations ($N = 42$) that used similar methodology.^{24,25} The AUC_{pop} estimate was the primary parameter used to compare the age groups by way of a ratio and 95% confidence interval (CI) for children in the current study/historical patients. Descriptive summary statistics were calculated for the other pharmacokinetic parameters. Safety data were evaluated by tabulating adverse experiences and by clinical assessment of laboratory data.

Pharmacokinetic Model

Pharmacokinetic analysis was conducted by a population-based approach using a fixed, 3-time point sampling schedule to conserve the amount of blood required to meet study objectives. As in previous pediatric studies of montelukast,^{24,25} a nonlinear, mixed-effects, 1-compartment model with first-order absorption and elimination provided a good fit of the data.²⁷ The structure of the model was prespecified and had been used historically in the montelukast development program to estimate pharmacokinetic parameters in pediatric patients.²⁸

Nonlinear Model Fitting

A nonlinear mixed-effects pharmacokinetics/statistical model was used to estimate the AUC_{pop} and standard error (SE) in the patients in the present study and in those 3 to 24 months of age who were previously studied.^{24,25} In this model, the natural logarithm ($\ln$) of AUC and elimination rate constant were random effects, and the $\ln$ absorption rate constant was fixed. In this study, the actual sampling times relative to dose were used. The nonlinear mixed-effects model was fitted to the pediatric data using the SAS procedure NLMIXED. To find appropriate starting values that would lead to convergence, historical population estimates were first used as starting values for the algorithm with the appropriate settings for the random and fixed effects.²⁵

Empirical Bayes estimates for AUC extrapolated to infinity ($AUC_{0-\infty}$) were used to calculate individual estimates for this parameter in participants in the present study and for patients aged 3 to 24 months from previous studies. Empirical Bayes estimates for $AUC_{0-\infty}$ for patients aged 3 to 6 months²⁵ were comparable to those for patients aged 6 to 24 months²⁴; therefore, these 2 age groups were pooled when calculating individual estimates for $AUC_{0-\infty}$ for patients aged 3 to 24 months. The individual estimates obtained were then plotted to show their association with the covariates of weight and age. Empirical Bayes estimates were also used for plotting individual estimated concentration-versus-time profiles for each patient.

The assumption of normality of the residuals from the model for the fitting for patients aged 1 to 3 months were tested using the Shapiro-Wilk test and by graphical methods. The residuals failed the Shapiro-Wilk test ($P < .050$) but passed visual inspection using graphical methods, indicating that the results may not have been influenced by any violation of these assumptions. The random effects for Cl/F passed both the Shapiro-Wilk test and visual inspection using graphical methods. Shapiro-Wilk normality test for the random effects for the equilibrium constant (k_c) was borderline significant. Therefore, the interindividual error estimates for k_c may not be well characterized by the model used. The limit of statistical significance accepted for all statistical analyses was $\alpha = 0.05$.

Post-hoc Analyses

When it was determined that population estimates for AUC_{pop} and C_{max} for patients aged 1 to 3 months

Table I Patient Demographics and Baseline Characteristics

Characteristic (n = 12)	
Mean age, mo (range)	1.5 (1-2)
Number of patients by age	
1 month	6
2 months	6
Gender, n	
Boys	7
Girls	5
Race, n	
Hispanic	11
White	1
Mean weight, kg (range)	5.0 (3.9-6.2)
Mean height, cm (range)	55.7 (51.0-60.0)

differed from those observed in patients aged 3 to 24 months, post-hoc analyses were performed, normalizing empirical Bayes estimates for $AUC_{0-\infty}$ and C_{max} to dose and body weight (to 1 mg/kg) over the complete range of age for all patients (ie, 1-24 months, including those in the current study and historical data from patients aged 3-24 months).

RESULTS

Of 20 patients screened for inclusion in the study, 12 met the inclusion criteria and were randomized to 1 of the 2 treatment groups (group A or B). Five subjects were randomized to group A (montelukast 4 mg/montelukast 4 mg/montelukast 8 mg) and 7 subjects to group B (montelukast 4 mg/placebo/ placebo). Baseline characteristics of randomized patients are displayed in Table I. One patient was discontinued in period 2 because of noncompliance, and 11 completed the study. One other patient missed receiving 1 dose of study drug during period 2; otherwise, patients were in compliance with study drug administration and study-related procedures.

Pharmacokinetics

Population estimates for area under the concentration-time curve after administration of a single 4-mg dose of montelukast oral granules for patients aged 1 to 3 months from the current study and for patients aged 3 to 6 months and 3 to 24 months (pooled data) from previous studies are presented in Table II.^{24,25} Compared with values in the older infants, AUC_{pop} was 3.6 times higher for the younger infants who

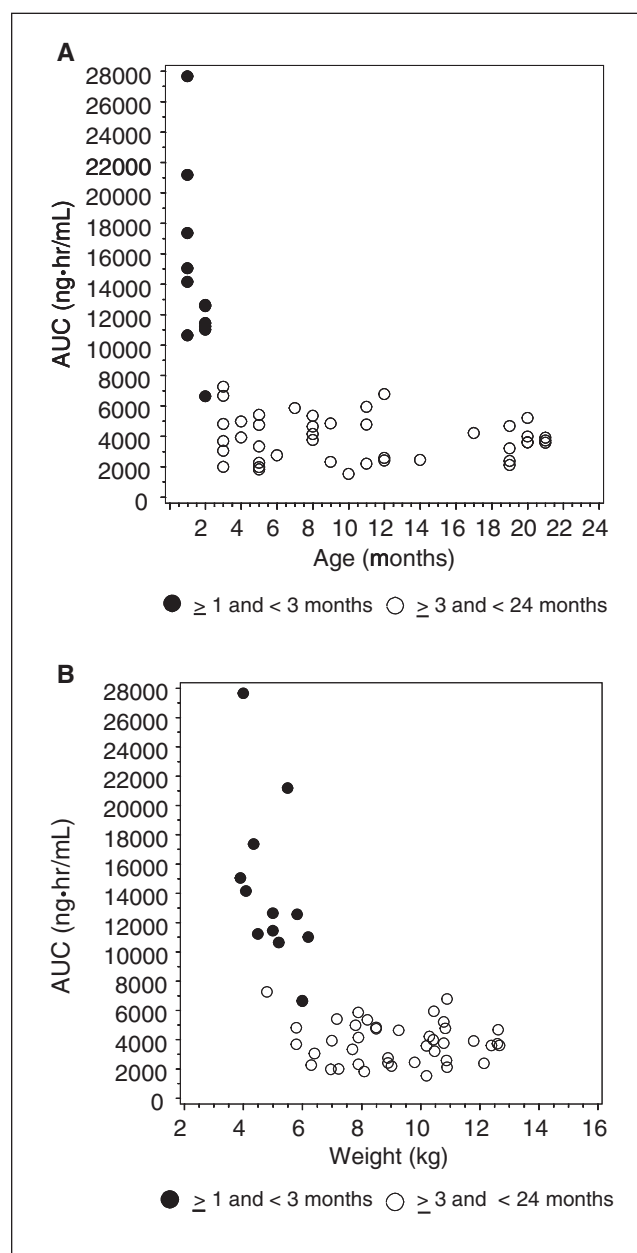


Figure 1. Individual $AUC_{0-\infty}$ Bayes estimates for montelukast versus age (A) and weight (B) in pediatric patients aged 1 to 24 months.

participated in the current study. Individual $AUC_{0-\infty}$ Bayes estimates for montelukast were plotted against age (Figure 1A) and weight (Figure 1B) for patients aged 1 month to 24 months old. An apparent significant ($P < .001$) inverse correlation was found between $AUC_{0-\infty}$ estimates versus age (Pearson correlation coefficient = -0.51) and weight (correlation coefficient = -0.63).

Table II Population Estimate of AUC for a Single Dose of Montelukast 4 mg as Oral Granules in Infant Patients

Population Age, mo	N	AUC _{pop} , ng-hr/mL ^a	95% CI	Population Mean Ratio (95% CI) ^b
1 to 3 (current study)	12	13 195.7 (2309.8)	7543.9-18 847.6	
3 to 6 (historical values) ^c	14	3644.3 (481.5)	2534.0-4754.6	3.62 (2.26-5.80)
3 to 24 (historical values) ^d	42	3629.2 (243.1)	3136.2-4122.1	3.64 (2.49-5.30)

AUC, area under the concentration-time curve; AUC_{pop}, population area under the concentration-time curve; CI, confidence interval.

a. Values are mean (standard error).

b. AUC of current study/historical values; back-transformed from the log scale.

c. Historical data.¹⁹

d. Combined historical data.^{19,20}

Table III Population Estimates of Pharmacokinetic Parameters for a Single Dose of Montelukast 4 mg as Oral Granules in Infant Patients

Population Age, mo	N	C _{max} , ng/mL	T _{max} , hr	t _{1/2} , hr	Cl/F, mL/min
1-3	12	1234.6 ± 196.4 (754.1-1715.1)	3.2 ± 0.6 (1.7-4.6)	1.20 ± 0.48 (0.02-2.39)	5.1 ± 0.9 (2.9-7.2)
3-6 ^a	14	561.1 ± 78.0 (381.3-741.0)	2.1 ± 0.4 (1.1-3.1)	0.94 ± 0.38 (0.05-1.82)	18.3 ± 2.4 (12.7-23.9)
3-24 ^b	42	582.3 ± 47.4 (486.2-678.4)	1.9 ± 0.3 (1.3-2.5)	0.75 ± 0.20 (0.34-1.17)	18.4 ± 1.2 (15.9-20.9)

Values are mean ± standard error (95% confidence interval).

C_{max}, maximum plasma concentration; T_{max}, time to C_{max}; t_{1/2}, apparent elimination half-life; Cl/F, clearance after oral administration where F = oral availability.

a. Historical data.¹⁹

b. Combined historical data.^{19,20}

Other pharmacokinetic parameters of montelukast for patients in the current study (aged 1-3 mo) and historical data from older infants are displayed in Table III. In patients 1 to 3 months of age, the population estimate for C_{max} was approximately 2.1 times higher; the population estimates for T_{max} and apparent t_{1/2} were slightly greater; and the population estimate for Cl/F was lower than in historical patients aged 3 to 6 months and 3 to 24 months.

Post-hoc Analyses

Although a trend was observed for AUC to be higher in younger patients in the present study (1-3 months of age) than in patients aged 3 to 24 months, post-hoc analysis indicated the trend was less pronounced than in the original analysis when estimates were dose-normalized to 1 mg montelukast/kg of body weight; individual estimates are plotted against age or weight (Figure 2). As with AUC, the trend for higher C_{max} in younger patients (1-3 mo) versus that for patients 3 to 24 months of age was less pronounced when estimates were dose-normalized to 1 mg montelukast/kg of body weight (Figure 3).

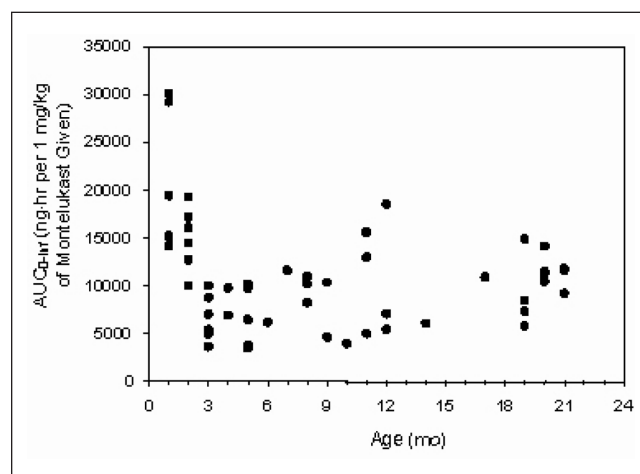


Figure 2. Individual dose-normalized AUC_{0-∞} Bayes estimates (1 mg montelukast/kg body weight) versus age in pediatric patients 1 to 24 months of age.

Safety and Tolerability

Six patients had a total of 10 clinical adverse experiences, including conjunctivitis, wheezing, and

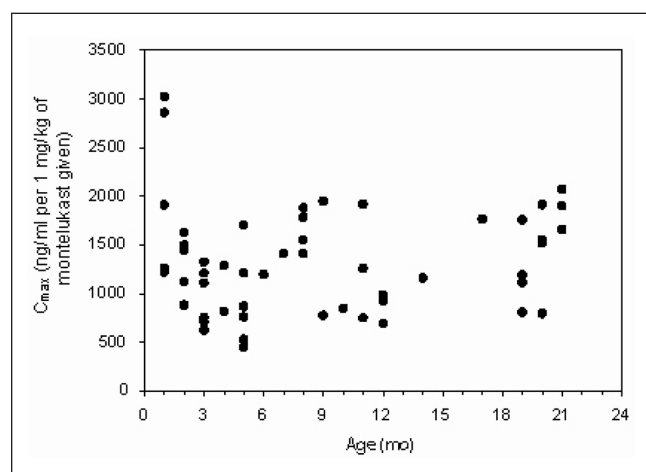


Figure 3. Individual dose-normalized C_{max} Bayes estimates (1 mg montelukast/kg body weight) versus age in pediatric patients 1 to 24 months of age.

cyanosis, during administration of montelukast 4 mg (period 2); genital fungal infection and viral diarrhea during administration of montelukast 8 mg (period 3); upper respiratory tract congestion, viral upper respiratory tract congestion, and vomiting during administration of placebo; and diarrhea and pyrexia on days 37 and 18, respectively (poststudy). None of the adverse experiences was considered by the investigator to be serious or related to the study drug. The intensity of the adverse experiences was considered mild or moderate, and all patients recovered.

Laboratory adverse experiences were limited to mild increases in serum aspartate aminotransferase (AST) in 3 patients, all from the same study site. For one of these patients, the increase was observed on day 14 (final dose of montelukast 8 mg), and increases for a second patient were reported on day 14 (final dose of montelukast 8 mg) and on days 24 and 32 (poststudy). Aspartate aminotransferase increases for the third patient were detected on day 14 (final dose of placebo) and on day 41 (poststudy). The increases were ≤ 2.2 times the upper limit of normal, and values returned toward normal limits at poststudy follow-up sampling. The investigator considered all of these laboratory adverse experiences to be possibly or probably drug related, but none was considered serious. High individual AUC values were not correlated with increased AST values.

DISCUSSION

This study is the first to examine pharmacokinetics, safety, and tolerability of montelukast oral granules in infants younger than 3 months of age. The patients

enrolled in the study had active bronchiolitis or a history of bronchiolitis and asthma-like symptoms. The pharmacokinetic data obtained after administration of a single 4-mg dose of montelukast oral granules were compared with historical values from older infants aged 3 to 24 months who also had received montelukast 4-mg oral granules.

Dose selection for montelukast in the present study was based on existing pharmacokinetic, pharmacodynamic, and safety data generated from prior investigations.²³⁻²⁵ Previous pediatric studies demonstrated that the 4-mg oral dose of the montelukast oral granules was well tolerated in 3- to 6-month-old infants with either active viral bronchiolitis or a history of bronchiolitis with current asthma-like symptoms²⁵ and in 6- to 24-month-old children with asthma.²⁴ In addition, a 5-mg chewable tablet (crushed) formulation of montelukast was well tolerated in 3- to 36-month-old children with bronchiolitis.²³ Data from previous studies in infants and young children led us to conclude that a dose smaller than 4 mg would not be a likely candidate for efficacy evaluation in pediatric bronchiolitis.²³ In view of this information and adult data that demonstrate dose-independent pharmacokinetics of montelukast in adults,²⁸ we elected to assess pharmacokinetics and safety/tolerability of 2 montelukast doses (4 mg and 8 mg) within a given infant, thereby generating data for a range of systemic exposures. Therefore, since the pharmacokinetics of montelukast are linear within this range in adults, the 8-mg dose was also evaluated in the present study.²⁸

The current study implemented a population pharmacokinetic approach with only 3 postdose sampling time points (due to the limited blood volume that could be obtained from this age group) selected on the basis of previous pharmacokinetic studies in pediatric patients that used a similar approach.^{24,25} A nonlinear, 1-compartment pharmacokinetic model with first-order absorption and elimination was chosen to fit the data in the current study. Overall exposure to montelukast after a single 4-mg dose of oral granules was approximately 3.6 times higher in 1- to 3-month-old patients than in historical patients aged 3 to 24 months.^{24,25} The AUC_{pop} ratio was 3.62 for patients aged 1 to 3 months compared with that for patients aged 3 to 6 months and 3.64 for patients aged 1 to 3 months compared with patients aged 3 to 24 months from previous studies. Correspondingly, the population estimate for Cl/F in the younger infants (5.1 mL/min) was approximately 3.6 times lower than that in 3- to 24-month-old patients (18.4 mL/min).

A trend (higher AUC) was observed in patients aged 1 to 3 months versus values for infants aged 3 to 24 months; however, when individual $AUC_{(0-\infty)}$ estimates for each patient were dose-normalized to 1 mg montelukast/kg of body weight and plotted against age and weight, this trend was less pronounced, suggesting smaller body weight can partially account for the higher systemic exposure in patients aged 1 to 3 months when given a 4-mg dose of montelukast. A similar result was obtained when C_{max} was corrected for montelukast dose and age.

Available data suggest that montelukast is eliminated through multiple pathways, including oxidation and glucuronidation. In vitro data indicate that the cytochrome P450 (CYP) enzymes 3A4 and 2C9 are involved in the oxidative metabolism of montelukast.²⁹ Although CYP3A4 activity increases rapidly after birth, it is estimated that the levels of CYP3A4 in 1-month-old infants are only about 30% to 40% of adult levels, reaching adult levels at 3 to 12 months of age.³⁰⁻³⁴ Cytochrome enzyme 2C9 levels are low in the first month of life and can vary up to 35-fold from birth to age 5 months, reaching adult levels by about 6 months of age.³⁴⁻³⁶ Although developmental expression of the phase II enzymes (uridine diphosphate [UDP]-glucuronosyltransferase [UGT]) involved in the glucuronidation of montelukast is less well understood, there is evidence suggesting UGT levels are considerably reduced in newborns, reaching adult levels between 2 months and 3 years of age.^{34,35,37,38} All of these factors combined might partially explain the higher and more variable exposure (ie, AUC) of montelukast observed in the current study of young infants compared with historical values in older infants. These findings are consistent with those observed for other drugs that are metabolized similarly. For example, the clearance of cisapride, which is primarily metabolized by CYP3A4, is reduced and the AUC increased in neonates and young infants (eg, those aged 0 to 3 months) compared with those in older children and adults.³⁹ The clearance of morphine, which undergoes primary glucuronidation by UGT2B7, typically reaches adult levels between 2 and 6 months of age but can take up to 30 months in some children.^{35,37}

The population estimate for C_{max} in this infant population was approximately 2.1 times higher than in older infants (3 to 24 months of age); this finding is likely attributable to the correlation of age and body size. Compared with values for older infants, the population estimate T_{max} in the current study was slightly later, and the population estimate

$t_{1/2}$ was slightly longer. However, these observed differences are not likely to be clinically meaningful based on the wide therapeutic index established for montelukast.²⁸

Montelukast (4 mg and 8 mg) was generally well tolerated by 1- to 3-month-old infants after single- and multiple-dose administration. All clinical adverse experiences reported were considered not serious and not drug related. Increases in AST observed in 3 patients were mild (no more than 2.2 times the upper limit of normal), and values returned toward normal limits during poststudy sampling. Subsequent to completion of the present study, in a double-blind, double-dummy, multicenter clinical study of children aged 3 to 24 months hospitalized with physician-diagnosed RSV-bronchiolitis, montelukast (4- or 8-mg dose) did not show a treatment effect on post-RSV-bronchiolitic respiratory symptoms.⁴⁰ Safety and tolerability profiles of montelukast at both doses were generally comparable to those of placebo in that study of 3- to 24-month-old children.

In conclusion, assessment of the effect of age on the pharmacokinetics of montelukast among infants aged 1 to 24 months is consistent with what has been reported regarding the developmental dependence and acquisition of function for enzymes responsible for the biotransformation of montelukast. Considering the known and expected age-related differences in body weight associated with normal growth and development, higher systemic exposures of montelukast were observed in infants aged 1 to 3 months compared with older infants and children after administration of a fixed 4-mg dose in both age groups. Nonetheless, based on extensive prior safety experience and a wide therapeutic margin with montelukast in children as young as 6 months of age,⁴¹ it is our contention that the available data do not support the necessity of dosing montelukast on a mg/kg basis in infants younger than 3 months of age. Further investigation would be needed to establish the appropriate fixed dose of montelukast in children younger than 3 months of age to produce the desired treatment effect and the degree of systemic exposure that mirrors the exposure in older children and adults.

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