

The Journal of Clinical Pharmacology

<http://www.jclinpharm.org>

Pharmacokinetics of Montelukast in Asthmatic Patients 6 to 24 Months Old

Elizabeth Migoya, Gregory L. Kearns, Alan Hartford, Jamie Zhao, Janet van Adelsberg, Carol A. Tozzi, Barbara Knorr and Paul Deutsch

J. Clin. Pharmacol. 2004; 44; 487

DOI: 10.1177/0091270004264970

The online version of this article can be found at:

<http://www.jclinpharm.org/cgi/content/abstract/44/5/487>

Published by:



<http://www.sagepublications.com>

On behalf of:

[American College of Clinical Pharmacology](#)

Additional services and information for *The Journal of Clinical Pharmacology* can be found at:

Email Alerts: <http://www.jclinpharm.org/cgi/alerts>

Subscriptions: <http://www.jclinpharm.org/subscriptions>

Reprints: <http://www.sagepub.com/journalsReprints.nav>

Permissions: <http://www.sagepub.com/journalsPermissions.nav>

Pharmacokinetics of Montelukast in Asthmatic Patients 6 to 24 Months Old

Elizabeth Migoya, PharmD, Gregory L. Kearns, PharmD, PhD, FCP, Alan Hartford, PhD, Jamie Zhao, PhD, Janet van Adelsberg, MD, Carol A. Tozzi, PhD, Barbara Knorr, MD, and Paul Deutsch, MD, PhD

Montelukast is a cysteinyl leukotriene receptor antagonist approved for the treatment of asthma for those ages 1 year old to adult. The purpose of this study was to evaluate the pharmacokinetic comparability of a 4-mg dose of montelukast oral granules in patients ≥ 6 to < 24 months old to the 10-mg approved dose in adults. This was an open-label study in 32 patients. Population pharmacokinetic parameters included estimates of AUC_{pop} , C_{max} , and t_{max} . Results were compared with estimates from adults (10-mg film-coated tablet [FCT]). Dose selection criteria were for the 95% confidence interval (CI) for the AUC_{pop} estimate ratio

(pediatric/adult 10 mg FCT) to be within comparability bounds of (0.5, 2.00). The AUC_{pop} ratio and the 95% CI for children compared with adults were within the predefined comparability bounds. Observed plasma concentrations were also similar. Based on systemic exposure of montelukast, a 4-mg dose of montelukast appears appropriate for children as young as 6 months of age.

Keywords: Montelukast; asthma; pediatrics; pharmacokinetics
Journal of Clinical Pharmacology, 2004;44:487-494
 ©2004 the American College of Clinical Pharmacology

Cysteinyl leukotrienes (LTC_4 , LTD_4 , LTE_4) are bioactive mediators released by eosinophils, mast cells, and other proinflammatory cells in the airways. These compounds mediate part of the pathophysiology associated with asthma responsible for causing bronchoconstriction, excess mucus secretion, increased vascular permeability, airway eosinophilia, and smooth muscle proliferation.¹⁻⁴ Montelukast is a potent leukotriene receptor antagonist that blocks the action of the cysteinyl leukotrienes.⁵ In controlled clinical trials, montelukast has been shown to reduce the signs and symptoms associated with asthma in adults,⁶

children ages 6 to 14 years old,⁷ and pediatric patients ages 2 to 5 years old.⁸ Montelukast attenuates exercise-induced bronchoconstriction in adults⁹ and children.¹⁰

Chronic asthma in children often begins in infancy or early childhood and is associated with inflammation of the airways^{11,12} and with the production of cysteinyl leukotrienes.^{13,14} It is recommended that treatment for asthma begin early to control inflammation and potentially reduce the deterioration of lung function over time.¹⁵ Currently, therapeutic options for anti-inflammatory controller therapy for small children are limited because of difficulties associated with drug administration (aerosol delivery systems) and concerns related to growth suppression produced by corticosteroids.¹⁶⁻¹⁸

Previous studies with montelukast have demonstrated an improvement in asthma symptoms in adult⁶ and pediatric^{7,8} patients. Since the clinical expression and pathology of asthma are similar in children and adults,^{15,19} it is reasonable to assume that providing a similar level of systemic exposure to montelukast in young children comparable to levels associated with efficacy in adults would result in a favorable clinical response. The strategy of the current study accomplished this comparison of exposures in children to those in adults. Such an approach obviated the need for

From Merck Research Laboratories, Rahway, New Jersey (Dr. Migoya, Dr. Hartford, Dr. Zhao, Dr. van Adelsberg, Dr. Tozzi, Dr. Knorr, Dr. Deutsch); Division of Pediatric Pharmacology and Medical Toxicology, Children's Mercy Hospitals and Clinics, Kansas City, Missouri (Dr. Kearns); and Departments of Pediatric and Pharmacology, University of Missouri-Kansas City, Kansas City, Missouri (Dr. Kearns). Support by a grant from Merck Research Laboratories, Rahway, New Jersey. Dr. Migoya, Dr. Hartford, Dr. van Adelsberg, Dr. Tozzi, Dr. Knorr, Dr. Deutsch, and Mr. Zhao are employed by Merck Research Laboratories; Dr. Kearns was an investigator in this study and received compensation from Merck Research Laboratories. Submitted for publication August 27, 2003; revised version accepted February 15, 2004. Address for reprints: Elizabeth Migoya, PharmD, Merck Research Laboratories, 126 East Lincoln Avenue, Rahway, NJ 07065.
 DOI: 10.1177/0091270004264970

more extensive and classical pharmacokinetic and/or dose-ranging studies of montelukast in very young children. To date, such an approach has been used successfully to establish the age-appropriate doses of montelukast that are both well tolerated and efficacious for pediatric patients 2 to 5²⁰ and 6 to 14 years of age.²¹

Treatment of asthma in the youngest patients is limited by the lack of age-appropriate formulations that are convenient to administer. A well-tolerated controller medication with proven efficacy that was easy to give to patients would meet the medical needs of children younger than 24 months old. This study determined an appropriate dose of a new formulation of montelukast oral granules using a population pharmacokinetic analysis of the drug following single-dose administration in asthmatic patients ≥ 6 to < 24 months old.

METHODS

Patients

Study participants were boys or girls ≥ 6 months to < 24 months of age who were between 6 and 15 kg total body weight and within the 5th to 95th percentile of height for weight. Patients had a history of physician-diagnosed asthma, including ≥ 3 discrete episodes of wheezing after 8 weeks of age with episodes separated by a symptom-free interval of at least 7 days or asthma-like symptoms (including but not limited to cough, wheezing, and shortness of breath) with a history of bronchiolitis requiring chronic anti-inflammatory controller therapy. Patients had to have been on solid food for at least 1 month and had to be in good health, including no evidence of pulmonary symptoms, prior to study entry.

Patients were excluded if they had a clinically significant disease/condition other than asthma/reactive airway disease, surgery within 8 weeks, unresolved signs and symptoms of an upper respiratory tract infection, or an upper respiratory tract infection within 1 week of the study. Participants were also excluded if they had taken astemizole within 3 months; terfenadine, loratadine, and/or oral or parenteral corticosteroids within 14 days; theophylline within 10 days; or any oral β -agonists within 24 hours prior to study drug administration or had received drugs or natural products associated with induction or inhibition of cytochrome P450 (CYP) enzyme metabolism within 1 month of study entry. Written informed consent, approved by the respective institutional review boards or ethical review committees for each investigational site,

Table I Schedules for Obtaining Blood Samples for a Single 4-mg Dose of Montelukast Oral Granules

Group	n	Blood Sampling Time (h)						
		0	2.5	3	5	8	12	24
A	17	X	X		X		X	
B	15	X		X		X		X

was obtained from the legally authorized representative of each patient.

During the study, patients were allowed to use inhaled albuterol, inhaled cromolyn, and inhaled corticosteroids if required. These medications were administered by a nurse or physician at the study site.

Study Design

This was a multicenter, open-label, single-dose population pharmacokinetic study performed at five study sites in the United States and in South America. Montelukast (4-mg oral granules) was administered to each patient with 1 tbs (approximately 15-18 g) of applesauce obtained from a single vendor. Patients were randomly assigned to one of two possible sampling schedules (A or B) (Table I). Blood samples for pharmacokinetic analysis (four samples each in schedule A and B, 3-mL volume each) were obtained from an indwelling venous cannula up to 24 hours after drug administration depending on patient assignment. At the discretion of the investigator, patients were admitted into the study unit on the evening preceding drug administration and remained until the 12-hour blood sample was obtained. Patients assigned to schedule B, requiring a 24-hour sample, were required to return to the study unit for this blood sample.

These sampling schedules were selected based on the ability to accurately estimate the AUC of montelukast in adult subjects compared to the AUC determined from the complete disposition profile (13-point concentration-time curves). The two 4-point (1 predose and 3 postdose) samples minimized the amount of blood required for sampling in the pediatric age group studied. Each schedule was selected so that the time points bracketed the mean time of maximum observed plasma concentration ($t_{\max}$) of 3.4 hours observed in the adult subjects and provided sufficient data to reliably estimate the apparent terminal elimination rate constant and the 24-hour postdose plasma concentration. A similar strategy was used to assess the

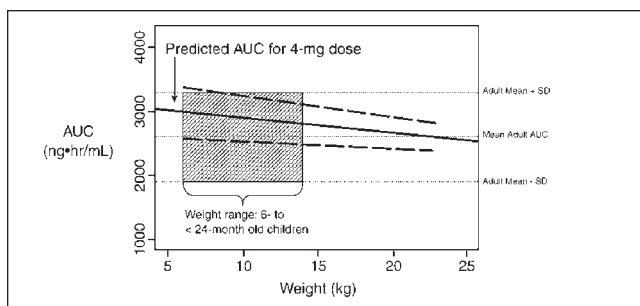


Figure 1. Weighted linear regression analysis of AUC versus weight extrapolated from weighted regression lines using data from previously completed pharmacokinetic studies. Dashed lines represent the 95% confidence band. Shaded area represents the range of median weights for ≥ 6 - to < 24 -month-old patients (based on National Center for Health Statistics weight tables).

pharmacokinetics of the 4-mg chewable tablet (CT) in 2- to 5-year-old patients.²⁰

Dose Selection

A 4-mg dose was selected for evaluation in the current study based on a weighted linear regression of the plotted AUC versus weight from previous pharmacokinetic studies in adults (10-mg film-coated tablet [FCT]) and pediatric patients (4-mg and 5-mg CT) (Figure 1). The predicted mean AUC and 95% confidence band, based on a 4-mg dose, were within one standard deviation (SD) of the reference mean $AUC_{0-\infty}$, except at the very low end of the weight range, where the upper boundary of the 95% confidence band was slightly greater than one SD above the reference. The predicted AUC values were obtained using 6-month to 24-month age-appropriate weights of 6 to 15 kg. Given the wide therapeutic index and to avoid underdosing, the 4-mg dose was selected as an estimate of the appropriate dose for pharmacokinetic evaluation in ≥ 6 - to < 24 -month-old asthmatic patients.

Pharmacokinetics

Population pharmacokinetic modeling differs from the subject-specific modeling used in adult studies with montelukast. In population modeling, only one estimate for each pharmacokinetic parameter is found and represents the typical behavior of a group of subjects. The values obtained by subject-specific modeling and population modeling are not identical; however, since they are both estimates representing the same parameter, they are clinically comparable. The population pharmacokinetic approach in this study employed a nonlinear, mixed-effect, one-compartment model with

first-order absorption and elimination fitted to the available montelukast plasma concentration-time data. This approach was based on the assumption of linear pharmacokinetics for montelukast previously observed in pediatric²¹ and adult patients.²² The pharmacokinetic model and its validation have been described elsewhere.²³

Statistical Methods

The pharmacokinetic parameters estimated included the population AUC, as well as population estimates for C_{max} and t_{max} . The apparent elimination half-life ($t_{1/2}$) was estimated using a linear mixed-effects model and concentration at 24 hours postdose (C_{24h}) from the mean of the observed values for this parameter. The population estimate of apparent oral clearance (CL/F) was also determined using the nonlinear mixed-effects model. Adequacy of the 4-mg dose in young children was assessed by comparison of the AUC_{pop} after administration of the oral granules in patients ≥ 6 to < 24 months to the AUC_{pop} historical data following administration of a single 10-mg FCT of montelukast in adults—the optimum adult dose selected based on dose-ranging studies.^{22,24} The AUC_{pop} was computed based on the population estimates of the above parameters and was compared with adult historical data analyzed similarly. The 95% confidence interval (CI) for the AUC_{pop} ratios (pediatric/adult values) were calculated for ≥ 6 - to < 24 -month-old patients. Although not a prespecified primary endpoint, AUC_{pop} ratios were also calculated for the subgroups ≥ 6 to < 12 months old and ≥ 12 to < 24 months old. The 95% CI for the AUC_{pop} ratio (pediatric/adult) was then evaluated against the prespecified comparability bounds of (0.50, 2.00). No bounds were prespecified for the subgroup comparisons. After a determination of a normal distribution for AUC_{pop} values, the natural logarithm of the values from the 4-mg oral granules were compared to the 10-mg FCT data using an unpaired, two-tailed test. The montelukast CL/F and elimination rate constant values were assumed to have log-normal distributions, each centered on a population mean, while the absorption rate constant was assumed to be the same across all subjects within a cohort. Instead of estimating these parameters for each subject, this population-modeling approach estimates the population mean based on the distributional assumption. Descriptive summary statistics were used to express the population pharmacokinetic parameters for montelukast in the study cohort. Safety and tolerability were evaluated by tabulating adverse experiences and by clinical assessment of laboratory data.

Table II Patient Demographics and Baseline Characteristics

	≥ 6 to < 24 Months	≥ 6 to < 12 Months	≥ 12 to < 24 Months
Number of patients	32	14	18
Age, median (range), months	14 (6-23)	9 (6-11)	18 (12-23)
Male % of patients	41	64	28
Weight, median (range), kg	10.4 (7.9-13.4)	9 (7.9-10.8)	11 (8.9-13.4)
Height (range), cm	77 (67-86.6)	72 (67.0-78.5)	81 (73.0-86.6)

Safety Evaluations

Clinical laboratory tests (hematology and serum chemistry) were performed 36 hours prior to randomization, at 24 hours postdose, and again at 3 to 5 days postdose. A physical examination, including height and weight, was performed 36 hours prior to randomization and at the 3- to 5-day poststudy visit. All patients had laboratory safety tests collected within 36 hours prior to dosing on day 1 of the study, except for 1 patient who had tests at 48 hours prior to dosing. Vital sign measurements, including blood pressure, heart rate, respiratory rate, and oral or tympanic temperature, were evaluated 3 hours prior to administration of montelukast, four times during the 24-hour sampling period, and once again at the 3- to 5-day poststudy visit. Adverse experiences were monitored throughout the 24-hour study period and for 14 days following completion of treatment. Spontaneously reported adverse experiences were recorded by the investigator, who determined the severity and causal relationship to study medication.

RESULTS

Patients

Patient characteristics are summarized in Table II. A total of 32 patients received a 4-mg dose of the oral granule formulation of montelukast and were included in the safety analysis. Of the 32 patients, 26 had sufficient data that could be evaluated for pharmacokinetic analysis. Of the 6 patients whose data were not evaluated, 1 did not completely consume the dose, 1 vomited shortly after receiving the dose, and 2 did not have a 12-hour blood sample obtained consequent to loss of vascular access. Two patients were excluded from the pharmacokinetic analysis because analysis could not be performed using a fixed-absorption rate constant due to their relatively low 3-hour and high 8-hour postdose plasma montelukast concentrations.

Pharmacokinetics

The AUC_{pop} estimates for pediatric patients and adults are given in Table III. The AUC_{pop} estimates were 3226.6 ng•h/mL after administration of a single 4-mg dose of the oral granules to ≥ 6- to < 24-month-old pediatric patients, as compared to 2569.0 ng•h/mL after administration of a single 10-mg dose of the FCT to adults. The AUC_{pop} ratio for infants ≥ 6 to < 24 months of age compared to adults was 1.26, with a 95% CI of (1.02, 1.54); these values are well within the prespecified comparability bounds of (0.50, 2.00). The AUC_{pop} ratios for the age-based subgroups also were contained within the comparability interval, although these criteria were not prespecified (Table III). The population estimate for CL/F for montelukast clearance was approximately 3-fold lower ($p = 0.05$) in pediatric patients (20.7 ± 1.6 mL/min) compared to the estimate for adults (64.9 ± 4.2 mL/min), consistent with similar AUC values despite a 2.5-fold difference in the dose (4 mg and 10 mg, respectively) (Table IV). There were no significant differences in montelukast CL/F between the age-specific subgroups ≥ 6 to < 12 months old and ≥ 12 to < 24 months old (Table IV). The population estimates for C_{max} and t_{max} and the mean values for $t_{1/2}$ and C_{24h} are included in Table V. The population estimate for C_{max} was approximately 2-fold greater in the ≥ 6- to < 24-month-old group (514.4 ng/mL) as compared to the estimate from the adult population (279 ng/mL). The population average value for t_{max} demonstrated an absolute difference of approximately 1 hour earlier in pediatric patients compared to adults. Mean values for $t_{1/2}$ were roughly comparable between the pediatric patient subgroups or between the entire pediatric patient cohort (3.4 h) and that from the adult reference population (4.1 h), with a trend suggestive of a slightly shorter $t_{1/2}$ in the pediatric patients. The mean C_{24h} values were similar between pediatric patients and adult subjects, despite the 2.5-fold lower difference in the absolute montelukast dose given to the pediatric pa-

Table III Summary Statistics for AUC_{pop} (ng•h/mL) of Montelukast after Administration of a Single 4-mg Dose of the Oral Granules to Pediatric Patients and of 10-mg Film-Coated Tablet in Adults

Population	n	AUC _{pop} (ng•h/mL)	Population Mean Ratio 95% CI (Pediatric/Adult)
Adult subjects	16	2,569.0 ± 165.7	
Pediatric			
≥ 6 to < 24 months old	26	3,226.6 ± 250.0	1.26 (1.02, 1.54)
≥ 6 to < 12 months old	12	3,470.9 ± 499.3	1.35 (0.97, 1.87)
≥ 12 to < 24 months old	14	3,039.3 ± 212.5	1.18 (0.97, 1.44)

Values are ± standard error of the mean; CI, confidence interval, back-transformed from the log scale; AUC_{pop}, area under the concentration-time curve determined by population pharmacokinetic analysis.

Table IV Summary Statistics for Population Apparent Clearance of Montelukast after Administration of a Single 4-mg Dose of the Oral Granules to Pediatric Patients and of a 10-mg Film-Coated Tablet in Adults

Population	n	CL/F (mL/min)	95% CI
Adult subjects	16	64.9 ± 4.2	(55.8, 73.9)
Pediatric			
≥ 6 to < 24 months old	26	20.7 ± 1.6	(17.3, 24.0)
≥ 6 to < 12 months old	12	19.2 ± 2.8	(13.0, 25.5)
≥ 12 to < 24 months old	14	21.9 ± 1.5	(18.6, 25.3)

Values are ± standard error of the mean; CL/F, population clearance; CI, confidence interval.

Table V Summary Statistics for Population Estimates of C_{max}, t_{max}, and t_{1/2}, and observed C_{24 h} for Montelukast after Administration of a Single 4-mg Dose of the Oral Granules to Pediatric Patients and of a 10-mg Film-Coated Tablet in Adults

Population	n	95% CI			
		Population C _{max} (ng/mL)	Population t _{max} (h)	Population t _{1/2} (h)	Observed C _{24 h} (ng/mL)
Adult subjects	16	279.0 (222, 336)	3.4 (3.0, 3.8)	4.1 (3.7, 4.5)	9.7 (7.6, 11.8)
Pediatric ≥ 6 to < 24 months old	26	514.4 (425, 604)	2.2 (2.0, 2.5)	3.4 (3.0, 3.8)	8.2 (4.6, 11.8)
≥ 6 to < 12 months old	12	583.5 (392, 775)	2.1 (1.4, 2.7)	3.2 (2.4, 4.1)	9.1 (2.1, 16.1)
≥ 12 to < 24 months old	14	470.1 (380, 560)	2.3 (2.0, 2.7)	3.5 (3.0, 3.9)	7.3 (2.1, 12.5)

n for C_{24h} is 16, 12, 6, and 6, respectively. CI, confidence interval. t_{1/2} was calculated using a linear mixed-effects model, whereas T_{max} and C_{max} were determined using a nonlinear mixed-effects model.

tients (4 mg) as compared to the adult reference population (10 mg). Scatter plots of the individual estimates for the AUC, estimated from time 0 to infinity (AUC_{0-∞}) from the pediatric patients, revealed no apparent association of AUC with either age or weight of the ranges of the patients enrolled in the study (data not shown).

Population pharmacokinetic data for montelukast from the present investigation and from previously published studies conducted in children^{20,21} and adults²² were used to simulate systemic exposure as a function of age and formulation. Figure 2 illustrates a

population fit of the montelukast plasma concentration-time data after administration of a single 4-mg dose of the oral granules to ≥ 6- to < 24- month-old patients, following administration of a single 4-mg CT to children 2 to 5 years old and after a single 10-mg FCT to adults. Plasma-concentration profiles after administration of montelukast as 4-mg oral granules or as 4-mg CT are similar, with a greater peak concentration observed for oral granules and CT formulations compared to 10-mg FCT in adults. The simulated trough (24 h postdose) plasma concentrations were comparable for the 10-mg

FCT in adults, the 4-mg CT in 2- to 5-year-olds, and the 4-mg oral granules in the ≥ 6 - to < 24-month-old patients (Figure 2).

Tolerability and Safety

A total of 13 patients reported 22 adverse experiences. There were no serious adverse experiences related to montelukast. The most common adverse experience was diarrhea occurring in 6 children. There were three cases of diarrhea and two cases of somnolence of mild intensity that were judged by the investigator to be possibly or probably drug related. One serious adverse experience of dehydration occurred 7 days after drug administration. This case of dehydration was due to nausea and vomiting and was viewed by the investigator to be definitely not related to montelukast. Three patients had four mild laboratory adverse experiences not considered to be drug related. One of the 3 patients had an increase in blood urea nitrogen from 13 to 24 mg/dL. This patient had the one serious adverse experience of dehydration due to nausea and vomiting. One patient had a decrease in neutrophil count 24 hours after montelukast administration that was not associated with a clinical adverse experience. Another patient experienced a slight, clinically insignificant reduction in hemoglobin at the 24-hour postdose evaluation. There were no clinically significant changes in vital sign determinations in any patient through the entire study period. In general, a single 4-mg dose of the oral granule formulation of montelukast was well tolerated in pediatric patients ages ≥ 6 to < 24 months old.

DISCUSSION

The pharmacokinetic results for this study demonstrated that a 4-mg dose of montelukast oral granules provided a systemic exposure for pediatric patients ≥ 6 to < 24 months of age similar to that of the clinically effective 10-mg FCT in adults. Thus, examination of the AUC_{pop} data lends pharmacokinetic support for the use of the 4-mg dose of oral granules in these young asthmatic patients.

Reports of asthma presenting early in life provided justification for the current study in infants.^{25,26} Similarities in the pathophysiology of asthma between pediatric and adult patients^{15,19} prompted the selection of the population pharmacokinetic dose-finding approach for montelukast in patients ≥ 6 to < 24 months of age that targeted a predefined comparability interval (0.50, 2.00). This interval was initially determined from classic studies that defined the exposure-response rela-

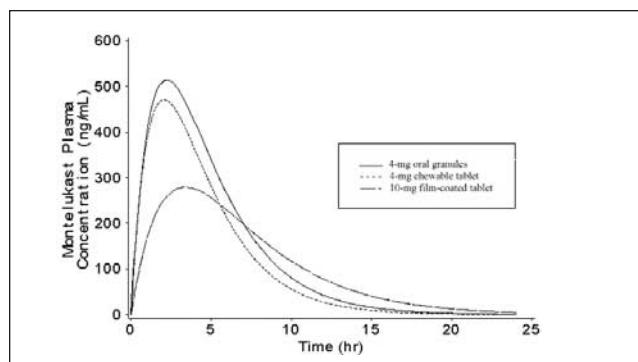


Figure 2. Population pharmacokinetic profile of fitted montelukast plasma concentration-time data after administration of single doses of the 4-mg oral granules to ≥ 6 - to < 24-month-old patients, the 4-mg chewable tablet to 2- to 5-year-old patients, and the 10-mg dose of the film-coated tablet to adults.

tionship for the drug.²² In addition, the population pharmacokinetic approach comparing the 90% CI of the AUC_{pop} ratio with the (0.50, 2.00) interval was used for montelukast dose selection to support the 4-mg CT dose currently approved for 2- to 5-year-old patients with asthma.²⁰

There were no apparent age-associated differences for the population pharmacokinetic parameters of montelukast within the experimental population and no clinically meaningful differences when data from the pediatric patients were compared to historical population pharmacokinetic data for adults (Tables III and V). The AUC_{pop} for the ≥ 6 - to < 24-month-old patients (3226.6 ng•h/mL) is approximately 25% greater than the adult estimate; however, montelukast has a wide therapeutic index,^{22,27} and unexpected toxicities would not be associated with this extent of systemic exposure in pediatric patients following the 4-mg dose. In addition, the pharmacokinetic profile (AUC_{pop}) for ≥ 6 - to < 24-month-old patients was similar to that for the 5-mg CT in 6- to 8-year-old patients (2928 ng•h/mL) and for the 10-mg FCT in 9- to 14-year-old patients weighing > 45 kg (3528 ng•h/mL).²¹

Potential dissolution differences between an oral granule formulation and the FCT could alter the rate of absorption of montelukast. The earlier t_{max} observed in the pediatric population receiving the oral granules compared to adults receiving the FCT is consistent with pharmacokinetic data from the CT formulation administered to adults,²¹ which is pharmaceutically similar to the oral granules. This would be clinically unimportant in pediatric patients since montelukast would be administered chronically, and its beneficial pharmacologic effects appear to be dependent on the

extent of systemic exposure rather than peak plasma concentrations. It is interesting to note that in 2- to 5-year-old patients, the population $C_{\max}$ estimate was also greater for the 4-mg CT compared with historical adult 10-mg FCT,²⁰ demonstrating the effect of formulation on the kinetics of drug absorption. Despite the differences in $C_{\max}$, a formulation-associated difference in overall montelukast exposure (reflected by AUC_{pop}) was not evident and, therefore, an impact on the efficacy and/or safety profile would not be expected. This assertion is supported, in part, by the demonstration of tolerability to montelukast in adults at $C_{\max}$ values up to 19.5 $\mu\text{g/mL}$ ²⁸—values more than 30 times those observed in the current study.

As recently reviewed by Muijsers and Noble,²⁹ montelukast is a substrate for both CYP3A4 and CYP2C9 (P450 cytochromes) with in vivo and in vitro evidence of similarity in the rate of biotransformation between children 6 to 11 years of age and adults. Previous pharmacokinetic data for other pharmacologic substrates of these two CYP enzymes suggest the potential for increased rates of intrinsic clearance in older infants and young children compared with older children and adults.³⁰ Assuming an average body weight of 70 kg for normal healthy adult subjects and 10 kg for this current population of infants (Table I), population CL/F values (Table IV) normalized for weight yielded parameter estimates of approximately 0.92 mL/min/kg and 2.1 mL/min/kg, respectively, for the adult and pediatric population, thereby suggesting a slightly increased clearance of montelukast in young infants. However, comparison of the elimination $t_{1/2}$ values revealed average values for the pediatric patients in the current study that were only slightly shorter (30 min) in the infants compared to historical data in adults (Table V). In addition, the value for CL/F was similar to that previously determined following administration of a 4-mg CT dose in children 2 to 5 years of age.²⁰ Comparability of the $C_{24\text{ h}}$ and AUC_{pop} values between these populations would also suggest that any apparent age-associated differences in the elimination of montelukast would not adversely influence the exposure-response relationship of the 4-mg dose in infants and young children.

Montelukast was generally well tolerated, with a favorable safety profile in patients ≥ 6 to < 24 months old. The single dose of montelukast administered to pediatric patients in this study had few adverse events attributable to montelukast. Safety and tolerability of montelukast have been demonstrated in adults in doses up to 800 mg²⁸ and at doses of 200 mg for 22 weeks.³¹ Montelukast has a safety profile similar to pla-

cebo in asthmatic patients 2 to 5 years old,⁸ 6 to 14 years old,⁷ and adults.⁶ There were three cases of diarrhea and two cases of somnolence possibly associated with montelukast in this study. In a recent 6-week study of montelukast 4-mg oral granules in infants ≥ 6 to < 24 months of age, diarrhea occurred in 10.9% of patients on active compound compared to 12.3% of patients receiving placebo.³² Similarly, in a 12-week study of montelukast in 2- to 5-year-old children with asthma, the incidence of diarrhea was 8% and 10% in the montelukast and placebo groups, respectively, and somnolence was not a common clinical adverse experience.⁸ Accordingly, these data would support the apparent absence of an age association with respect to the adverse event profile for montelukast.

In conclusion, this study determined that a single 4-mg dose of montelukast oral granules given to patients ≥ 6 to < 24 months of age provided systemic exposure (AUC_{pop}) similar to that of the clinically effective 10-mg FCT in adults. Thus, based on previous exposure-response data for montelukast, pharmacokinetic evidence supports the selection of the 4-mg dose in ≥ 6 - to < 24-month-old asthmatic patients.

The authors thank Theodore F. Reiss, MD, and Keith Gottesdiener, MD, for careful review of this manuscript. Investigators: Maria Lina Boza Costagliola, MD, Chile; Elida Dueñas Meza, MD, Colombia; Luis Miguel Franchi, MD, Peru; Renato T. Stein, MD, Brazil.

REFERENCES

1. Busse WW: The role of leukotrienes in asthma and allergic rhinitis. *Clin Exp Allergy* 1996;26:868-879.
2. Laitinen LA, Laitinen A, Haahtela T, Vilkkla V, Spur BW, Lee TH: Leukotriene E_4 and granulocytic infiltration into asthmatic airways. *Lancet* 1993;341:989-990.
3. Dahlen SE, Hedqvist P, Hammarstrom S, Samuelsson B: Leukotrienes are potent constrictors of human bronchi. *Nature* 1980;288:484-486.
4. Cohen P, Noveral JP, Bhala A, Nunn SE, Herrick DJ, Grunstein MM: Leukotriene D_4 facilitates airway smooth muscle cell proliferation via modulation of the IGF axis. *Am J Physiol* 1995;269:L151-L157.
5. De Lepeleire I, Reiss TF, Rochette F, Botto A, Zhang J, Kundu S, et al: Montelukast causes prolonged, potent leukotriene D_4 -receptor antagonism in the airways of patients with asthma. *Clin Pharm Ther* 1997;61:83-92.
6. Reiss TF, Chervinsky P, Dockhorn RJ, Shingo S, Seidenberg B, Edwards TB, for the Montelukast Clinical Research Study Group: Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma. *Arch Intern Med* 1998;158:1213-1220.
7. Knorr B, Matz J, Bernstein JA, Nguyen H, Seidenberg BC, Reiss TF, et al: Montelukast for chronic asthma in 6- to 14-year-old children: a randomized, double-blind trial. *JAMA* 1998;279:1181-1186.
8. Knorr B, Franchi LM, Bisgaard H, Vermeulen JH, LeSouef P, Santanello N, et al: Montelukast, a leukotriene receptor antagonist,

for the treatment of persistent asthma in children aged 2 to 5 years. *Pediatrics* 2001;108(3):E34.

9. Leff JA, Busse WW, Pearlman D, Bronsky EA, Kemp J, Hendeles L, et al: Montelukast, leukotriene-receptor antagonist, for the treatment of mild asthma, and exercise-induced bronchoconstriction. *N Engl J Med* 1998;339:147-152.

10. Kemp JP, Dockhorn RJ, Shapiro GG, Nguyen HH, Reiss TF, Seidenberg BC, et al: Montelukast once daily inhibits exercise-induced bronchoconstriction in 6- to 14-year-old children with asthma. *J Pediatr* 1998;133:424-428.

11. Stevenson EC, Turner G, Heaney LG, Schock BC, Taylor R, Gallagher T, et al: Bronchoalveolar lavage findings suggest two different forms of childhood asthma. *Clin Exp Allergy* 1997;27:1027-1035.

12. Chedevergne F, Le Bourgeois M, de Blic J, Scheinmann P: The role of inflammation in childhood asthma. *Arch Dis Child* 2000;82(Suppl. II):II6-II9.

13. Sampson AP, Green CP, Spencer DA, Piper PJ, Price JF: Leukotrienes in the blood and urine of children with acute asthma. *Ann NY Acad Sci* 1991;629:437-439.

14. Azevedo I, de Blic, Scheinmann P, Vargaftic BB, Bachelet M: Enhanced arachidonic acid metabolism in alveolar macrophages from wheezy infants. *Am J Respir Crit Care Med* 1995;152:1208-1214.

15. Global Initiative for Asthma: *Global Strategy for Asthma Management and Prevention*. NIH Pub. No. 95-3659. Bethesda, MD: National Heart, Lung, and Blood Institute, 1995.

16. The Childhood Asthma Management Program Research Group: Long-term effect of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343:1054-1063.

17. Simons FER: A comparison of beclomethasone, salmeterol, and placebo in children with asthma. *N Engl J Med* 1997;337:1659-1665.

18. Doull IJ, Freezer NJ, Holgate ST: Growth of prepubertal children with mild asthma treated with inhaled beclomethasone dipropionate. *Am J Respir Crit Care Med* 1995;151:1715-1719.

19. Busse W, Banks-Schlegel SP, Larsen GL: Childhood- versus adult-onset asthma. *Am J Respir Crit Care Med* 1995;151:1635-1639.

20. Knorr B, Nguyen HH, Kearns GL, Villaran C, Boza ML, Reiss TF, et al: Montelukast dose selection in children ages 2 to 5 years: comparison of population pharmacokinetics between children and adults. *J Clin Pharmacol* 2001;41:612-619.

21. Knorr B, Larson P, Nguyen HH, Holland SD, Reiss TF, Chervinsky P, et al: Montelukast dose selection in 6- to 14-year-olds: comparison

of single-dose pharmacokinetics in children and adults. *J Clin Pharmacol* 1999;39:786-793.

22. Altman LC, Munk Z, Seltzer J, Noonan N, Shingo S, Zhang J, et al, for the Montelukast Asthma Study Group: A placebo-controlled, dose-ranging study of montelukast, a cysteinyl leukotriene-receptor antagonist. *J Allergy Clin Immunol* 1998;102:50-56.

23. Nguyen H, Zhang J, Larson P, Knorr B: Use of the population one-compartment model to design a study to best estimate the AUC with limited number of time points per patient. *Clin Pharmacol Ther* 1998;63:195.

24. Bronsky EA, Kemp JP, Zhang J, Guerreiro D, Reiss TF: Dose-related protection of exercise-induced bronchoconstriction by montelukast, a cysteinyl leukotriene-receptor antagonist, at the end of a once-daily dosing interval. *Clin Pharmacol Ther* 1997;62:556-561.

25. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Norgan WJ: Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332:133-138.

26. Martinez FD: Recognizing early asthma. *Allergy* 1999;54(Suppl. 49):24-28.

27. Noonan MJ, Chervinsky P, Brandon M, Zhang J, Kundu S, McBurney J, et al: Montelukast, a potent leukotriene receptor antagonist, causes dose-related improvements in chronic asthma. *Eur Respir J* 1998;11:1232-1239.

28. Schoors DF, De Smet M, Reiss T, Margolskee D, Cheng H, Larson P, et al: Single dose pharmacokinetics, safety and tolerability of MK-0476, a new leukotriene D₄-receptor antagonist, in healthy volunteers. *Br J Clin Pharmacol* 1995;40:277-280.

29. Muijsers RBR, Noble S: Montelukast: a review of its therapeutic potential in asthma in children 2 to 14 years of age. *Pediatr Drugs* 2002;4:123-139.

30. Leeder JS: Pharmacogenetics and pharmacogenomics. *Pediatr Clin North Am* 2001;48:765-781.

31. Singulair® (montelukast sodium) tablets, chewable tablets, and oral granules. Whitehouse Station, NJ: Merck & Co., 2002.

32. van Adelsberg J, Wei LX, Knorr B, Moy J, Weinstein S, Maspero J, et al: Safety and tolerability of montelukast (sprinkles) in 6 to 24 month old asthmatic patients. *Am J Respir Crit Care Med* 2002;165:A744.