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J. Clin. Pharmacol. 2001; 41; 612

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Montelukast Dose Selection in Children Ages 2 to 5 Years: Comparison of Population Pharmacokinetics between Children and Adults

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Montelukast, a leukotriene receptor antagonist, has demonstrated efficacy and tolerability in the treatment of asthma in patients age 6 years and older. The purpose of this open, one-period, multicenter population pharmacokinetic study was to identify a chewable tablet (CT) dose of montelukast for administration to children ages 2 to 5 years with asthma, yielding a single-dose pharmacokinetic profile (area under the plasma concentration-time curve [AUC]) comparable to that of the 10 mg film-coated tablet (FCT) dose in adults. Because patient numbers were small and the volume of blood that could be collected from indi-

vidual 2- to 5-year-old patients was limited, a population pharmacokinetic approach was used to estimate population AUC (AUC_{pop}). The 4 mg CT dose of montelukast was well tolerated and yielded an AUC_{pop} (2721 ng•h/mL) similar to that of the adult AUC_{pop} (2595 ng•h/mL) observed after a 10 mg FCT dose. These results support the selection of a 4 mg once-daily CT dose of montelukast for future efficacy and safety studies in children ages 2 to 5 years with asthma.

*Journal of Clinical Pharmacology, 2001;41:612-619
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Asthma is one of the most common chronic diseases in children worldwide, and its prevalence is increasing.¹⁻³ The disease is primarily a chronic inflammatory disorder characterized by airways obstruction and inflammation, increased vascular permeability, excess mucus production, eosinophil infiltration, and changes in smooth muscle contraction.^{2,4} Although less is known about asthma in children than in adults, evidence suggests that its expression is similar in the two populations.^{1-3,5,6}

It is currently understood that cysteinyl leukotrienes (CysLTs) play a central role in the pathogenesis of asthma.⁷⁻⁹ CysLTs are potent bronchoconstrictors present in the airways that are released during challenges causing bronchoconstriction.¹⁰⁻¹⁴ Data suggest that the CysLTs also stimulate the production of airways secretions, cause microvascular leakage, and enhance eosinophilic migration into airways.^{15,16} Moreover, drugs that selectively block leukotriene synthesis or receptor binding have proven effective in clinical studies for ameliorating symptoms of chronic asthma.^{17,18}

Montelukast, a selective CysLT₁-receptor antagonist,¹⁹ has demonstrated efficacy and tolerability in the treatment of chronic asthma in patients 6 years of age and older.²⁰⁻²⁴ In adults, a 10 mg dose of montelukast (film-coated tablet [FCT]) once daily in the evening produces improvement in measures of airways obstruction and patient-reported endpoints such as asthma symptoms and quality of life.²¹⁻²³ The adult dose of montelukast, selected by classic dose-ranging studies, was found to be the minimal dose producing the maximal response in the treatment of chronic asthma and attenuation of exercise-induced bronchoconstriction.

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tion.^{13,20,21,25} Bedtime dosing was designed to provide near-maximal plasma concentrations of montelukast coincident with the time (early morning hours) of maximal airways narrowing.²⁶

Because of technical and ethical considerations regarding drug testing in children, it is important to continue to develop ways to use information gained in adults for testing new treatment strategies in the pediatric population. Given that the clinical expression of asthma and its treatments are similar in children and adults, the dose of montelukast for children (ages 6-14 years) was selected by identifying the chewable tablet (CT) dose (5 mg once daily) that provided an overall systemic exposure (i.e., AUC) to montelukast in children similar to that in adults receiving a 10 mg FCT dose.²⁷ Subsequently, this approach to dose selection was validated when the efficacy and tolerability of the 5 mg CT dose of montelukast were confirmed in two studies in 6- to 14-year-old patients (one in chronic asthma and one in exercise-induced bronchoconstriction).^{26,27}

Previous adult and pediatric studies have demonstrated that there is little or no accumulation of montelukast and its metabolites. Therefore, single-dose studies may be used to compare the pharmacokinetics of montelukast across age groups.²⁷ Because the 2- to 5-year-old age range presents unique logistical challenges in achieving appropriate patient numbers and adequate plasma samplings (volume of blood) for classic pharmacokinetic studies, a population pharmacokinetic approach was used to estimate pharmacokinetic parameters of interest. Using a weighted linear regression analysis of AUC values versus weight with data from five previously completed pharmacokinetic studies, a 4 mg CT dose was predicted to provide an AUC in children ages 2 to 5 years similar to that of a 10 mg FCT dose in adults, provided there was no major change in drug disposition across the age ranges. Therefore, we hypothesized that the population AUC (AUC_{pop}) of montelukast after a 4 mg CT dose in patients ages 2 to 5 years would be similar to historical adult data collected after a 10 mg FCT dose and analyzed in similar fashion. The purpose of the present study, therefore, was to identify a CT dose of montelukast for administration to children ages 2 to 5 years with asthma, yielding a single-dose pharmacokinetic profile (i.e., AUC) comparable to the 10 mg FCT dose in adults.

METHODS

Patients

Enrolled patients were male or female children ages 2 to 5 years, with a history of physician-diagnosed

asthma. Patients weighed from 10 to 20 kg, were in otherwise good health, and were able to chew and subsequently swallow a tablet.

Written informed consent approved by the respective ethical review committees (Chile and Peru) or institutional review board (United States) was obtained from the parents or guardians of all patients.

The adult study, used as a source of historical adult data, enrolled healthy male volunteers between 18 and 45 years of age.²⁷

Study Design

This was an open, one-period, single-dose, multicenter study evaluating the population pharmacokinetics of a single oral 4 mg CT dose of montelukast in patients ages 2 to 5 years with asthma. The 4 mg CT dose of montelukast administered to patients in this study was estimated based on a weighted linear regression analysis of AUC values versus weight and was performed using data from five previously completed pharmacokinetic studies in adults, adolescents, and children (Figure 1). This analysis was based on the dose proportionality of both the CT and the FCT and the 20% greater AUC seen with the CT compared with the FCT.²⁷ By extrapolating the weighted regression to the weight range (10-20 kg) for patients ages 2 to 5 years, it was expected that a 4 mg CT dose would provide an AUC similar to that observed in the historical adult 10 mg FCT group. The study was conducted at three centers (one each in Chile, Peru, and the United States) over a 4-week period in 1997.

Patients were evaluated for study inclusion at a prestudy visit 4 to 7 days before drug administration, at which time a physical examination was performed, vital signs were recorded, and blood samples were collected for inclusion evaluation, safety assessment, and pretreatment montelukast plasma concentration assays.

Parents and guardians were instructed to withhold oral β -agonists for 24 hours and foods and beverages containing caffeine for 8 hours before study drug administration. Patients fasted beginning at midnight the night before the treatment day. Clear apple juice was permitted until 1 hour before drug administration, and free access to water was permitted at all times.

The 4 mg CT dose of montelukast (provided by Merck Research Laboratories [MRL], Rahway, NJ) was administered under observation, chewed, and followed by 50 mL of water. No food was permitted for 2 hours, when a snack was provided. An age-appropriate (both amount and composition) lunch and dinner were provided 4 and 8 hours after drug administration, respectively.

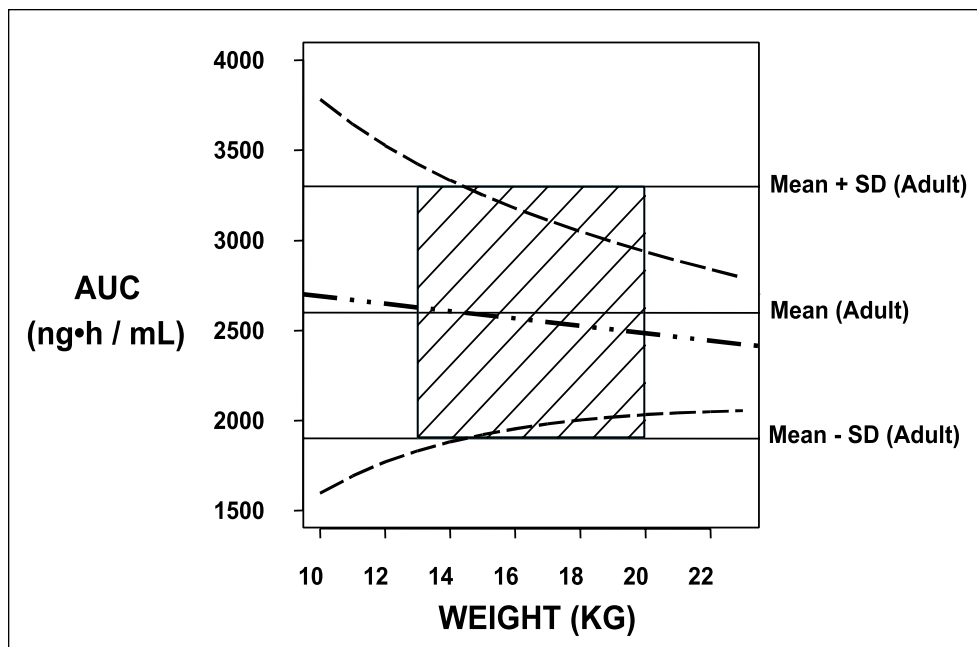


Figure 1. Weighted linear regression analysis of AUC versus weight extrapolated from weighted regression lines using data from five previously completed pharmacokinetic studies in adults, adolescents, and children (4 mg chewable tablet [CT] scenario). Weighted least squares regression line (long and short dashed line) with 95% confidence bands (long dashed lines). Crosshatched area represents the median of the weight for 2- to 5-year-old children (range: 13-20 kg [based on National Center for Health Statistics weight tables]).

Because the volume of blood that could be collected from individual patients was limited, patients were randomly allocated according to a computer-generated allocation schedule to one of two distinct plasma sampling schedules (with four sampling times in each schedule). All samples were obtained via an indwelling catheter or by venipuncture with topical anesthetic. Patients assigned to Sampling Schedule A had plasma samples at the prestudy visit (designated as time 0) and at 1.5, 4, and 12 hours after study drug administration. Patients assigned to Sampling Schedule B had plasma samples obtained at the prestudy visit (designated as time 0) and then at 2, 8, and 24 hours after study drug administration. These sampling schedules were prospectively selected to achieve a robust and efficient estimate of AUC_{pop} using a population pharmacokinetic model (described below) based on simulations performed using historical adult and pediatric pharmacokinetic data.²⁸

The adult study used as the source of historical adult data was a randomized, four-period, crossover study designed to compare the pharmacokinetic profile, dose proportionality, and safety of the CT and FCT formulations of montelukast. In this study, plasma concentrations for the 10 mg FCT dose were obtained before study drug administration and at 0.5, 1, 2, 4, 6, 8, 12, 16, and 24 hours after study drug administration. The study has been described in detail elsewhere.²⁷

Montelukast Analysis

Blood samples (3 mL/sample) were collected at designated times into tubes containing sodium heparin. Samples were immediately centrifuged; plasma was stored at -70°C and protected from exposure to light. Montelukast plasma concentration was determined using high-pressure liquid chromatography (HPLC) with fluorescence detection.²⁹ The assay had a lower limit of quantitation of 3 ng/mL. Data below the limit of quantitation were assigned a value of 0 ng/mL. All assays were performed at the MRL Drug Metabolism Department (West Point, PA).

Evaluation Criteria

Since montelukast was to be given chronically for the treatment of asthma and AUC was considered to be the pharmacokinetic measurement best representing systemic exposure to the drug, the primary evaluation criterion was the AUC_{pop} . AUC_{pop} was estimated using a pharmacokinetic model (described below) and then compared with estimated AUC_{pop} values from similarly analyzed historical adult data. Estimated population peak plasma concentration (C_{max}), time to population peak plasma concentration (t_{max}), and half-life ($t_{1/2}$) were also compared with historical adult values. Safety and tolerability in the current study were evaluated by recording adverse experiences and by clinical assess-

ment of laboratory tests (blood chemistry, complete blood count, and platelet count taken before study drug administration and 48 to 72 hours after study drug administration) performed at a central laboratory (Covance Laboratories, Indianapolis, IN).

Pharmacokinetic Analyses

A population pharmacokinetic approach using a nonlinear, mixed-effect, one-compartment pharmacokinetic model with first-order absorption and elimination was fitted to the available montelukast plasma concentration for both the pediatric 4 mg CT and historical adult 10 mg FCT pharmacokinetic data. The model and its validation have been described elsewhere.²⁸ Use of the pharmacokinetic model was based on the assumption that montelukast would exhibit linear pharmacokinetics in patients ages 2 to 5 years, as has been observed in adults and older pediatric patients.^{19,27}

Individual and population AUCs, individual and population elimination rates, and the individual population absorption rate, with corresponding variabilities, were estimated for both the pediatric and adult groups using the nonlinear, mixed-effect function in S-plus software (MATH Soft, Inc., version 3.4). The AUC_{pop} , C_{max} , and t_{max} , with corresponding 90% confidence intervals (CIs), were then estimated using the pharmacokinetic model. The $t_{1/2}$ for both the 4 mg CT pediatric and historical adult 10 mg FCT groups was derived by fitting a linear mixed-effect model to the log concentration data over time using the last two available time points per patient (four time points for the population) for the pediatric group and the last five available time points per patient for the historical adult group. The mean plasma trough levels for the pediatric and adult groups were computed using the available data at 24 hours after treatment.

Statistical Analyses

The natural logarithm of the AUC_{pop} values from the 4 mg CT pediatric group and the historical adult 10 mg FCT group were compared using a two-sample *t*-test. The 90% CI for the geometric mean ratio (pediatric/adult) was computed and compared with a prespecified interval of 0.5 to 2.0, which encloses a 50% difference in AUC_{pop} between pediatric patients and adults.

The study had 80% power that the 90% CI for the AUC_{pop} geometric mean ratio (pediatric/adult) would be contained within the range 0.71 to 1.41, assuming a true AUC_{pop} geometric mean ratio of 1.0 after single-dose administration using a two-sample *t*-test design.

Table I Patient Demographic and Baseline Characteristics

Number of patients	15	
Age, median (range), years	4	(2-5)
2 years old, number of patients (%)	5	(33)
3 years old, number of patients (%)	1	(7)
4 years old, number of patients (%)	2	(13)
5 years old, number of patients (%)	7	(47)
Male, number of patients (%)	7	(47)
Weight, median (range), kilograms	17	(12-22)
Height, median (range), centimeters	106	(84-118)
Ethnicity		
Caucasian, number of patients (%)	6	(40)
Black, number of patients (%)	3	(20)
Mestizo, number of patients (%)	6	(40)

RESULTS

Patients

Fifteen 2- to 5-year-old patients with asthma initiated and completed the study at three clinical centers. Patient characteristics are summarized in Table I. Eight of the 15 patients had a history of at least one medical condition other than asthma prior to randomization. The most common of these were conjunctivitis (4 patients) and a history of upper respiratory infection (4 patients). Seven of 15 patients had received asthma therapy within 30 days of the beginning of the study. The most common prior therapies were inhaled corticosteroids (beclomethasone, 4 patients; fluticasone, 1 patient) and albuterol (4 patients). Four of the patients received at least one concomitant medication, the most common of which was beclomethasone (3 patients).

Pharmacokinetics of Montelukast in Children Ages 2 to 5 Years versus Adults

Estimated AUC_{pop} in children versus adults. The estimates of AUC_{pop} for the 4 mg CT pediatric and the historical adult 10 mg FCT groups, using the population model, are shown in Table II. The geometric mean ratio (pediatric/adult) for AUC_{pop} was 1.05 with a 90% CI of (0.90, 1.22), indicating that the two population AUCs were comparable and fell within prespecified clinically meaningful bounds of (0.5, 2.0). In addition, a comparison of the AUC_{pop} for the 4 mg CT pediatric group with the AUC from zero to infinity ($AUC_{0-\infty}$) for the historical adult FCT group (calculated using con-

Table II Comparison of AUC_{pop} for 4 mg Pediatric CT and 10 mg Adult FCT Groups

Treatment	Number	Geometric Mean: AUC_{pop} $\pm$ SEM (ng•h/mL)	GMR: Pediatric/Adult	90% CI for GMR
4 mg pediatric CT	15	2721 $\pm$ 164	1.05	0.90-1.22
10 mg adult FCT (historical data)	16	2595 $\pm$ 165		

SEM, standard error of the mean; CT, chewable tablet; FCT, film-coated tablet; GMR, geometric mean ratio; CI, confidence interval.

ventional methodology) corroborates the findings from this analysis (geometric mean ratio [pediatric/adult] of 1.11 with a 90% CI of [0.94, 1.31]).

The observed and population plasma concentration profiles for the 4 mg CT pediatric and the historical adult 10 mg FCT groups are plotted in Figure 2. Note that the observed plasma concentration profile of the 4 mg CT pediatric group contains data from 7 or 8 of 15 patients at each time point (based on the sampling schedule), while the observed plasma concentration profile for the historical adult 10 mg FCT group contains data from all 16 patients at each time point.

Estimated population C_{max} , t_{max} , and $t_{1/2}$ in children versus adults. The population mean C_{max} values for the 4 mg CT pediatric group were larger than those of the historical adult 10 mg FCT group (Table III). The population mean t_{max} for the 4 mg CT pediatric group was shorter than that of the historical adult 10 mg FCT group. The mean values for C_{max} and t_{max} may also be in-

terpolated from Figure 2. The estimates of C_{max} and t_{max} obtained using the pharmacokinetic model were comparable to the mean observed C_{max} and t_{max} values for both the pediatric and historical adult groups. However, the coefficients of variation of C_{max} and t_{max} were lower in the 4 mg CT pediatric group compared with the historical adult 10 mg FCT group (53% vs. 76% and 56% vs. 71% for C_{max} and t_{max} , respectively).

The $t_{1/2}$ estimate of 3.2 hours, based on the last two time points per patient for the 4 mg CT pediatric group, was similar to, albeit somewhat lower than, that previously observed in the historic adult data used for comparison (Table III). Using the conventional computation method, the $t_{1/2}$ was 4.6 hours for the historical adult 10 mg FCT group. A lower trough plasma concentration (24 hours after treatment) was seen for the 4 mg CT pediatric group, based on the 7 patients with data available at this time point (mean $\pm$ SEM, 4.0 ng/mL $\pm$ 1.21) as compared with the 10 FCT adult group (9.67 ng/mL $\pm$ 0.98). This is consistent with the somewhat

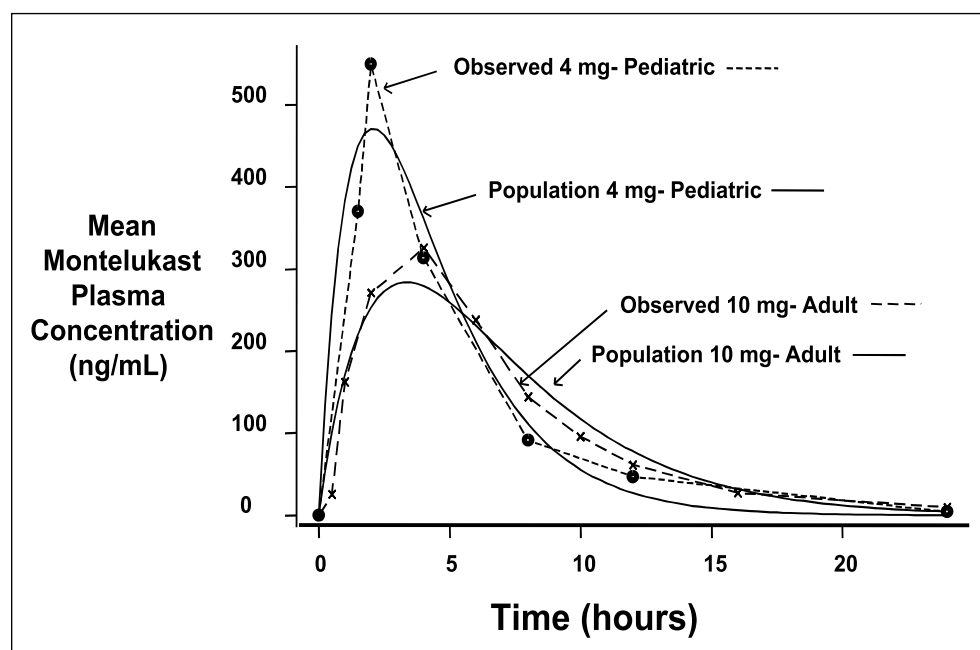


Figure 2. Mean observed and population plasma (predicted) concentration profiles for the 4 mg chewable tablet (CT) pediatric and the historical adult 10 mg film-coated tablet (FCT) groups. Pediatric and adult montelukast plasma concentration values were estimated over time using a nonlinear, mixed-effect pharmacokinetic model and compared with observed mean concentration values. Observed values were based on data from 16 adult patients at each time point; pediatric values were based on data from 7 or 8 patients at each time point (based on the sampling schedule).

Table III Comparison of Pediatric and Adult Estimated Population $C_{\max}$, $t_{\max}$, and $t_{1/2}$

Treatment	Number	Mean $C_{\max}$ $\pm$ SEM (ng/mL)	90% CI for $C_{\max}$	Mean $t_{\max}$ $\pm$ SEM (h)	90% CI for $t_{\max}$	$t_{1/2} \pm$ SEM (h)
4 mg CT pediatric	15	471 $\pm$ 65	362-580	2.07 $\pm$ 0.3	1.57-2.58	3.17 $\pm$ 0.2
10 mg FCT adult (historical data)	16	283 $\pm$ 54	194-374	3.36 $\pm$ 0.6	2.37-4.36	4.09 $\pm$ 0.1

SEM, standard error of the mean; CT, chewable tablet; FCT, film-coated tablet; CI, confidence interval; $C_{\max}$, peak plasma concentration; $t_{\max}$, time to peak plasma concentration; $t_{1/2}$, half-life.

more rapid elimination (shorter $t_{1/2}$) for montelukast in the pediatric patients in this study.

Safety and Tolerability

Three of the 15 patients participating in the study had an adverse experience (upper respiratory infection, 1 patient; diarrhea, 2 patients), two of which occurred while the patients were off the drug (greater than 24 hours postdose). There were no laboratory adverse experiences. There were no discontinuations due to an adverse experience.

DISCUSSION

We compared data from a pediatric population pharmacokinetic study with historical adult data to select a pediatric dose of montelukast for administration to children ages 2 to 5 years in clinical safety and efficacy studies. A 4 mg CT dose was well tolerated in these young patients and yielded a single dose AUC_{pop} comparable to that of a 10 mg FCT dose in adults, the optimum adult dose selected based on dose-ranging studies.^{20,25}

The clinical expression and treatment of asthma are similar in children and adults.^{1-3,5,6} This observation, encouraged by a 1994 U.S. Food and Drug Administration ruling,³⁰ provides the rationale for selecting a therapeutic dosage of montelukast based on identifying the CT dose providing systemic drug exposure (i.e., AUCs) similar to that of the clinical adult 10 mg FCT dose. Since montelukast was to be administered chronically for the treatment of asthma, AUC was considered to be the parameter best representing systemic exposure to the drug over time. This approach was previously used to select the 5 mg CT dose of montelukast for 6- to 14-year-old children.²⁷ Subsequently, the efficacy of the 5 mg dose was confirmed in a chronic asthma study²⁴ and an exercise challenge study.³¹ The same dose selection procedure was used in the present study to select a montelukast dose for 2- to 5-year-old children.

The population pharmacokinetic approach used enabled us to obtain accurate pharmacokinetic parameter estimates with sparse sampling in individual patients.²⁸ However, unlike many other pharmacokinetic population studies, which are geared toward the analysis of few data points in a large number of patients, this study applied the population approach to a situation involving small patient numbers (a situation commonly encountered in pediatric studies) with a prespecified, prospectively designed small number of samples determined at times, based on prior adult and pediatric pharmacokinetic data, to enrich the yield of pharmacokinetic data.^{28,32,33} It is our opinion that the population approach used in this study may be applicable to future pediatric pharmacokinetic studies with similar constraints to those we encountered on plasma sampling numbers.

The pharmacokinetic model used in this study was prospectively validated using historical adult and pediatric montelukast plasma concentration data.²⁸ In the model validation, it was determined that the estimates of AUC_{pop} and corresponding standard errors were similar to the mean AUCs and standard errors computed using conventional methodology (i.e., within 10% of each other). Furthermore, using the historical adult and pediatric data and the pharmacokinetic model, sampling schedules were prospectively selected that provided an estimate of AUC_{pop} within one standard deviation of the mean AUC obtained conventionally. Therefore, in this study, AUC_{pop} provides a reliable estimate of $AUC_{0-\infty}$ without a conventional range of plasma sampling time points. The comparison of estimated and observed AUCs shown in Figure 2 corroborates this assertion.

Although the pharmacokinetic model was selected to estimate AUC, the estimates of $t_{\max}$ and $C_{\max}$ obtained using the model were comparable to the corresponding mean observed values. The estimate of $t_{\max}$ was shorter and that of $C_{\max}$ was larger for the 4 mg CT pediatric group as compared with the historical adult 10 mg FCT

group. This result was consistent with previous studies of montelukast in both adults and children in which the CT exhibited a shorter $t_{\max}$ and larger $C_{\max}$ than the FCT.²⁷

Since montelukast will likely be administered as chronic therapy for the management of asthma, the observed difference in the estimates of $t_{\max}$ between the CT and the FCT is not considered to be clinically important. The difference in $C_{\max}$ between the 4 mg CT pediatric and historical adult 10 mg FCT groups is also not considered to be clinically important because it should not influence the clinical response to therapy or affect tolerability. Tolerability has been demonstrated at dosage levels well above 10 mg/day in adults, with $AUC_{0-\infty}$ and $C_{\max}$ values up to 173,000 ng•h/mL and 19.5 µg/mL, respectively.³⁴

Of note, the coefficient of variation for $C_{\max}$ and $t_{\max}$ was smaller for the 4 mg CT pediatric group compared with the historical adult 10 mg FCT group. This is consistent with data comparing a 10 mg CT with a 10 mg FCT in adults, in which the coefficient of variation for several pharmacokinetic parameters (including $C_{\max}$ and $t_{\max}$) was also smaller for the CT group than the FCT group (data on file at Merck Research Laboratories). Therefore, the observed difference in variability between the 4 mg CT pediatric group and the historical adult 10 mg FCT group seen in this study most likely represents a dosage form effect rather than an age effect.

The $t_{1/2}$ estimate for the 4 mg CT pediatric group was slightly shorter than the estimate for the historical adult group. However, the value was within the range of values seen in adult studies (2.7 to 5.5 hours) (data on file at Merck Research Laboratories). The mean trough value for the pediatric patients was lower than that seen in adults. Although trough levels may be important for the overall efficacy of some drugs, trough values have not been shown to correlate well with the overall efficacy of montelukast, especially clinical benefit throughout the dosing interval. In adult dose-ranging studies, montelukast caused clinically important improvements in measures of airways obstruction (FEV_1 and morning and evening peak expiratory flow) at doses as low as 2 mg once daily. Interestingly, the mean trough value of the 2 mg FCT in adults (0.6 ng/mL) was well below the trough value for the 10 mg FCT (9.7 ng/mL), the optimal dose. The observed trough value after administration of the 4 mg CT dose (4 ng/mL) in children ages 2 to 5 years is well above that observed after a 2 mg FCT dose in adults, a dose with demonstrated efficacy throughout the dosing interval.²¹ Therefore, it was expected that a 4 mg CT dose would provide efficacy at the end of a once-daily dosing interval.

The appropriateness of the 4 mg CT dose selection based on pharmacokinetics was subsequently confirmed by the results of a clinical efficacy and safety study in 689 children with asthma ages 2 to 5 years.^{35,36} Montelukast, 4 mg CT once daily at bedtime, demonstrated significant effects on multiple efficacy endpoints, including daytime and overnight asthma symptoms, confirming the efficacy of montelukast throughout a once-daily dosing interval.³⁵ Moreover, these findings were consistent with those of efficacy studies in adults and older children.²²⁻²⁴

In summary, administration of a single 4 mg CT of montelukast in patients ages 2 to 5 years was well tolerated and yielded a systemic exposure (AUC_{pop}) similar to that seen after the clinically effective 10 mg FCT dose in adults. Because the clinical expression of asthma is similar in children and adults, the results of this study suggested that a 4 mg CT dose of montelukast in these patients will be clinically similar to a 10 mg FCT dose in adults. The appropriateness of the 4 mg once-daily dose selection for children with asthma ages 2 to 5 years was subsequently confirmed by results of a clinical efficacy and safety study in this age group.^{35,36}

We acknowledge Raju D. Amin, BS, and Jamie Zhao, PhD, for performing the montelukast assays; Elizabeth Hillyer, DVM, for editorial assistance; and Lars Olof Eriksson, MSc, PhD, Merle A. Schneider, BS, and Gertrude P. Noonan, BA, for coordination of the study.

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