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Research Paper

A Population Pharmacokinetic Model for Montelukast Disposition in Adults and Children

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Purpose. The purpose was to develop a population pharmacokinetic model for montelukast after intravenous administration. Clinical trial simulations were conducted using the model developed to identify the lowest intravenous dose in 6- to 14-year-old children that would give montelukast systemic exposures that were comparable to those found to be associated with efficacy in adults.
Methods. Two clinical studies were conducted where montelukast was administered intravenously as a 7-mg dose to adults and as a 3.5-mg dose to children aged 6 to 14 years. Model development included defining the base pharmacostatistical model and investigating the effects of demographic variables [age and total body weight (TBW)] on the structural parameters, using a nonlinear mixed effect modeling approach.
Results. A linear three-compartment pharmacokinetic model was found to best describe the disposition of montelukast. Inclusion of TBW as a covariate caused a 35% and 63% decrease in the interindividual variabilities on clearance and central volume of distribution, respectively. Trial simulations suggested that a 5.25-mg intravenous dose of montelukast should be chosen in children aged 6 to 14 years.
Conclusions. The model developed can adequately describe the intravenous pharmacokinetics of montelukast and can be used as a useful tool for dose selection in pediatric subpopulations.

KEY WORDS: children; intravenous; model; montelukast; population pharmacokinetics.

INTRODUCTION

Montelukast sodium, the active ingredient in Singulair, is a selective leukotriene-receptor antagonist that inhibits the cysteinyl-leukotriene $CysLT_1$ receptor (1). A 10-mg film-coated tablet, 4- and 5-mg chewable tablets, and a 4-mg oral granule formulation in individual packets are approved for marketing in the United States and in several other countries for the treatment of chronic asthma and seasonal allergic rhinitis.

Cysteinyl-leukotrienes, lipid mediators released from inflammatory cells, produce airway edema, mucus secretion, and eosinophil migration; reactions associated with the major findings of airway inflammation in asthma (2–4). Cysteinyl-leukotrienes levels are thought to be elevated in patients with acute asthma, providing a rationale for treatment with anti-leukotriene agents during acute exacerbations. Short-acting β_2 agonists and corticosteroids are currently the standard treatments for acute asthma exacerbations (5). The intravenous formulation of montelukast is being developed as a single-dose, nonsteroidal agent, as an adjunct to standard therapy in order to provide immediate relief from an acute exacerbation of asthma. Furthermore, asthma in children is a similar disease to that in adults (6–9), and the prevalence of acute asthma in children is high, justifying the necessity for developing treatments for acute exacerbations in the pediatric population as well.

In a pilot study composed of 201 adult patients with chronic asthma, a 7-mg intravenous dose of montelukast was well tolerated, caused rapid bronchodilation, and was associated with significant reduction in the percentage of patients receiving acute administration of corticosteroids (10). Moreover, there was no additional benefit of a 14-mg dose compared to a 7-mg dose. It was also confirmed that no clinically meaningful differences exist between the 7-mg and 14-mg groups in terms of the incidence of adverse experiences. Therefore, it is projected that a dose in pediatric patients that provides exposures (AUC) comparable to those after a 7-mg intravenous dose in adults will be safe and efficacious.

The clinical pharmacokinetics (PK) of montelukast after oral administration have been studied extensively using conventional noncompartmental pharmacokinetic analyses (11–13). Montelukast is rapidly absorbed after oral administration and is extensively metabolized followed predominantly by elimination in bile (14). There are two studies that report the intravenous noncompartmental pharmacokinetics of montelukast in adults and the elderly (12,13). In these studies, the mean plasma terminal half-life of montelukast ranged from 4.5 to 6.7 h. Consistent with this terminal half-life, upon multiple dose administration, there is little accumulation of

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montelukast in plasma (12). The oral bioavailability is modestly high (~60% to 70%), and the pharmacokinetics of montelukast are nearly linear for oral doses up to 50 mg and for intravenous doses up to 18 mg in adults (12,13). The pharmacokinetics of montelukast have been reported to be similar in males and females (13). Montelukast pharmacokinetics in pediatric patients after oral dosing have been studied, and the sparse data collected have been modeled empirically using a one-compartment population PK model (15,16).

Our primary objectives were to investigate the population pharmacokinetics of montelukast after intravenous administration in adults and children and to describe the influence of patient covariates [age and total body weight (TBW)] on the interpatient variability in montelukast pharmacokinetics. We designed two clinical studies in which doses of 7 mg and 3.5 mg were administered intravenously to adults and children aged 6 to 14 years, respectively. PK data collected from these two studies were used to develop a population pharmacokinetic model for montelukast disposition. The model developed was used as a tool toward dose selection in a demographic subpopulation.

The strategy for pediatric dose selection involved using the model to identify the lowest intravenous dose in children aged 6 to 14 years that would provide a distribution of exposures similar to those after a 7-mg intravenous dose in adults. The optimal oral dose of 10 mg in adults has been shown to be associated with a mean AUC of approximately 2500 ng·h/ml (17), and therefore it was also targeted to achieve exposures at least as high as 2500 ng·h/ml in majority of the subjects. It is anticipated that this population PK model will serve as a useful tool in examining sparse data from other pediatric age groups as well in the future.

MATERIALS AND METHODS

Formulation

The intravenous formulation is lyophilized montelukast containing sodium carbonate as excipient. It is reconstituted prior to administration in a domestically available commercial vehicle containing 3.3% dextrose and 0.3% sodium chloride. This results in an isotonic solution with a pH of approximately 8.6 to 8.8. The resultant solution is light-sensitive and therefore is diluted in light-protected glass containers.

Study Design

Two clinical studies were conducted where in montelukast was administered as a single 7-mg intravenous dose (5-min infusion) to adults (study 1) and as a single 3.5-mg intravenous dose (5-min infusion) to 6- to 14-year-old pediatric patients (study 2). These studies were conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research. Study 1 was a double-blind, randomized, placebo-controlled, two-period, multicenter study in 25 patients with chronic asthma comparing a single 7-mg dose of intravenous montelukast with placebo over a 24-h observation period. Twelve patients participated in the pharmacokinetic evaluation, and were all included in the analysis of plasma drug concentrations. Blood samples were collected at predose, 0.08, 0.5, 1, 2, 4, 6, 8, 12, 16, and 24 h post-dose. The second study was an open-label, single-dose study in 12 asthmatic children aged 6 to 14 years. In this study, a single 3.5-mg intravenous dose of montelukast was administered, and blood samples were collected for pharmacokinetic evaluation at predose, 0.08, 0.5, 1, 2, 4, 8, 12, and 24 h post-dose. Three-milliliter blood samples were drawn into 3-ml venoject tubes containing sodium heparin as anticoagulant. Blood was centrifuged immediately, and the plasma fraction was transferred to a tube covered with aluminum foil. Samples were stored at −70°C.

Assay

Plasma samples were assayed by a high-performance liquid chromatography (HPLC) assay method (18). In this assay, montelukast is extracted from human plasma by protein precipitation and analyzed by HPLC with fluorescence detection. The lower limit of detection (LLOQ) is 3 ng/ml, and the calibration range is from 3 ng/ml to 964 ng/ml. The method is validated with satisfactory precision and accuracy. The accuracy and precision (within and between-run variability) were less than 9%. All assays were performed at the Merck Research Laboratories (MRL) Drug Metabolism Department (West Point, PA, USA).

Population PK Analysis

The population PK analysis was performed using the NONMEM (version V) computer program (19). The covariance subroutine was executed with each run to obtain the covariance matrix, correlation matrix, and standard errors of estimates. The first step was to define the base pharmacostatistical model and obtain Bayesian estimates of pharmacokinetic parameters. Next, exploratory analysis was performed using the Xpose software (20) to assess the base model and investigate the effects of covariates (age and TBW) on the various model parameters. Finally, the stepwise approach as described below was used to test the effect of the two covariates on various model parameters using the power model.

Pharmacostatistical Model

Two- and three compartment linear models were fitted to the multiexponential plasma concentration-time profiles using nonlinear mixed effects modeling with the first-order conditional estimation (FOCE) method. The intravenous infusion was modeled as a zero-order input over 5 min. A log-normal distribution on interindividual variability for all structural parameters was assumed, which translates to an exponential error model as follows:

$$P_{ij} = TVP_j \times \exp(\eta_{ij})$$

where P_{ij} is the jth parameter for the ith individual and TVP_j is the typical population estimate for the jth parameter. η_{ij} is the deviation of P_{ij} from TVP_j in the jth parameter for the ith individual. The interpatient variability η is assume to have a mean 0 and estimated variance ω^2.

The following error models for residual variability were evaluated:

1. Additive error model $C_{ik} = Pred_{ik} + \varepsilon_{\text{add}}$

Table I. Summary Statistics for Patient Characteristics (Age, TBW, and Height)[a]

	n	Mean	Standard deviation	Median	Range
Study 1					
Age (years)	12	42.8	14.5	45.5	19–68
TBW (kg)	12	72.8	11.7	71	60–98
Height (inch)	12	67.1	8.5	67.9	61.4–72.4
Study 2					
Age (years)	11	10.3	2.9	11	6–14
TBW (kg)	11	38.1	15.5	36.4	17.9–66.9
Height (inch)	11	56.8	8.5	56.8	43.7–74.5

[a] Includes only those patients who had blood samples for PK withdrawn.

2. Proportional error model $C_{ik} = Pred_{ik} \times (1 + \varepsilon_{prop})$
3. Combined additive and proportional error model $C_{ik} = Pred_{ik} + \varepsilon_{prop} \times Pred_{ik} + \varepsilon_{add}$

where C_{ik} and $Pred_{ik}$ are the measured and model-predicted concentration at the kth sampling time in the ith individual, respectively. The residual variability ε is a random variable with mean 0 and estimated variance σ^2. The residual variability describes errors arising from assay errors, sampling inaccuracies, and model misspecification.

Covariate Analysis

After arriving at the appropriate PK model, the potential influences of covariates (age and TBW) on montelukast disposition were tested. The minimum value of the objective function (OFV) resulting from NONMEM analysis without inclusion of any patient covariates (Base model) was used as a reference for covariate analysis. The potential relation between the empirical Bayes estimates of the PK parameters and covariates was investigated by graphical analysis. The forward selection method was used to build the full model in NONMEM. The effect of each covariate on each model parameter was defined by adding one covariate at a time on one parameter and recording the OFV. The most significant covariate was added to the model (base 1) and the process was repeated to finally arrive at the most complex model (base 2) that included all significant covariates on various parameters. The backward elimination method was then applied on the complex model to confirm the final model. Covariates were entered into the base model using a forward selection significance level of 0.05 and a backwards deletion criterion of 0.005. To investigate the relationship between the covariate and the structural parameter, both power (e.g., $TVP_j = \theta_{j1} \times TBW^{\theta j2}$) and linear models (e.g., $TVP_j = \theta_{j1} + \theta_{j2} \times TBW$) were tested, where TVP_j is the typical population estimate for the jth parameter.

Model Selection

The likelihood ratio test, Akaike information criteria (AIC), and goodness of fit plots were used for model discrimination. For accepting a model, the following criteria had to be met: 1) convergence of the minimization procedure and termination of the covariance step without warning messages, 2) decrease in OFV of 7.88 for one additional degree of freedom (significance level of 0.005) based on the log likelihood ratio which is approximately χ^2 distributed, 3) 95% confidence interval of the additional parameter not including zero, 4) residual standard error (RSE) (SE/mean × 100) of less than 50% for each estimated parameter (5) visual inspection of goodness-of-fit plots.

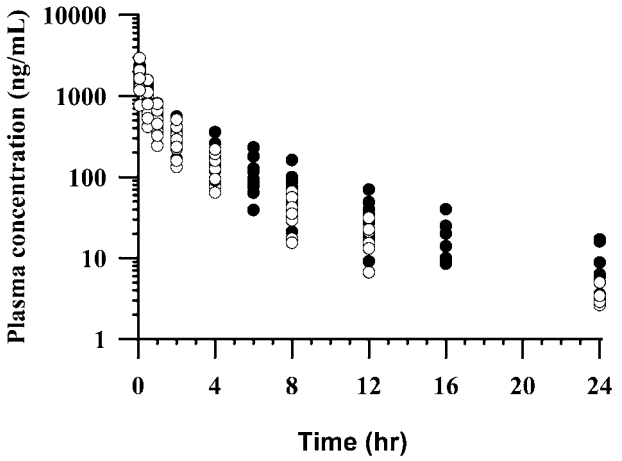

Fig. 1. Observed individual plasma concentrations of montelukast following administration of single IV doses of montelukast to adults and children aged 6 to 14 years. Solid circles represent plasma concentrations after a 7-mg intravenous dose in adults, and open circles represent plasma concentrations after a 3.5-mg intravenous dose in children aged 6 to 14 years.

Simulations

The final model was incorporated into the Pharsight Trial Simulator software Version 2.1.2. Simulations were performed to identify the lowest intravenous dose that would yield a distribution of exposures in children aged 6 to 14 years that were comparable to those obtained following a 7-mg intravenous dose in adults. A log-normal distribution of TBW

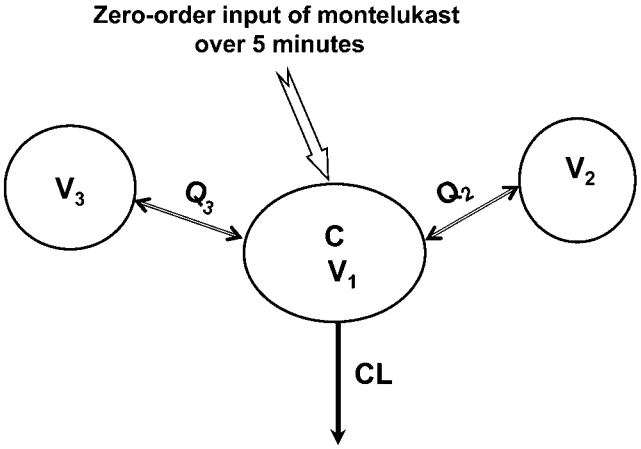

Fig. 2. Schematic of a three-compartment model with first-order elimination used to describe the disposition of montelukast. Estimated structural parameters included CL (elimination clearance from central compartment), V_1, V_2, and V_3 (volumes of the central and peripheral compartments), and Q_2 and Q_3 (distributional clearances between the central and peripheral compartments). C is the concentration of montelukast in the plasma/central compartment. The 5-min infusion was modeled as a 5-min zero-order input into the central compartment.

Table II. Summary of Models Tested in the Population Analyses

Covariate	ΔOFV[a]	p value
Forward selection		
Base model: No covariates and		
TBW on *CL*	–33.97	<0.005
TBW on V_1	–25.66	<0.005
TBW on V_3	–26.37	<0.005
Age on *CL*	–19.62	<0.005
Age on V_1	–12.3	<0.005
Age on V_3	–17.46	<0.005
Base 1: TBW on *CL* and		
TBW on V_1	–38.85	<0.005
TBW on V_3	–34.99	<0.005
Age on *CL*	–0.002	NS
Age on V_1	–20.4	<0.005
Age on V_3	–22.97	<0.005
Base 2: TBW on *CL* and V_1 and		
TBW on V_3	–32.36	<0.005, NA
Age on *CL*	–0.012	NS
Age on V_1	–0.013	NS
Age on V_3	–21.55	<0.005, NA
Backward elimination from base 2 (full model)		
TBW on *CL* and no effect on V_1	+38.85	<0.005
TBW on V_1 and no effect on *CL*	+47.16	<0.005
TBW on *CL* and V_1, set $\theta_2 = 1$	+12.81	<0.005
TBW on *CL* and V_1, set $\theta_1 = 1$	+10.20	<0.005

NS, not significant; NA, model not acceptable as standard errors associated with some parameters were greater than 50% and confidence interval included zero.

[a] Change in objective function value (OFV) upon addition of covariates (TBW and age) on each model parameter compared to the appropriate base model.

Table III. Final Population Parameter Estimates for Montelukast (Base 2/Full Model) Estimated by NONMEM

	Population estimate	RSE
$TVV_1 = \theta_{V1} \times TBW^{\theta 1}$		
θ_{V1} (ml)	156	40.7
θ_1	0.726	14.0
$TVCL = \theta_{CL} \times TBW^{\theta 2}$		
θ_{CL} (ml/h)	175	46.4
θ_2	0.635	18.7
V_2 (ml)	2180	16.7
V_3 (ml)	2610	10.8
Q_2 (ml/h)	256	17.3
Q_3 (ml/h)	2580	9.4
Interindividual variability (%)		
ω_{CL}	24.2	31.1
ω_{V1}	14.0	42.5
ω_{V3}	45.4	32.5
Residual variability		
σ_{add} (ng/ml)	3.7	23.4
σ_{prop}	10.4%	40.8

Relative standard error (standard error/mean × 100).

was assumed in children and adults. Based on historical Merck data (n = 61) in asthmatic patients aged 6 to 14 years, a mean of 39.8 kg and a standard deviation of 15.65 kg was used to describe the TBW distribution. This distribution is also consistent with literature published values in healthy children aged 6 to 14 years (21). A mean TBW of 80.1 and standard deviation of 29.7 kg was assumed to describe the weight distribution in adults aged 20 years and above (21). Simulations were also performed using a weight range of 20 to 51 kg which corresponds to the 50th percentile of TBW in boys and

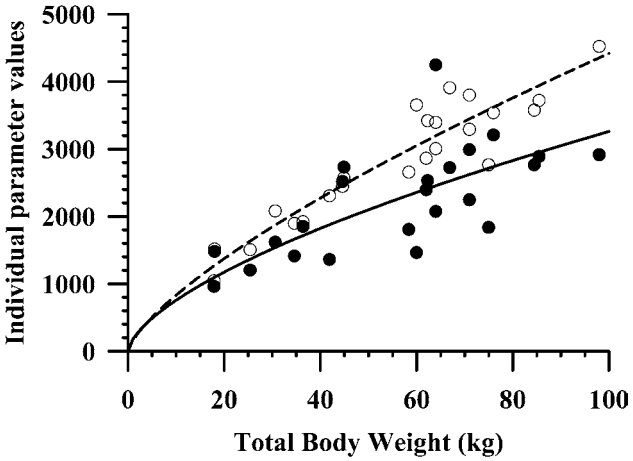

Fig. 3. Individual *CL* (ml/h) and V_1 (ml) estimates plotted against TBW (total body weight). Solid and open circles are individual Bayesian parameter estimates for *CL* and for V_1, respectively. The solid and dashed lines represent the population model predicted *CL* and V_1 in typical subjects of varying body weight.

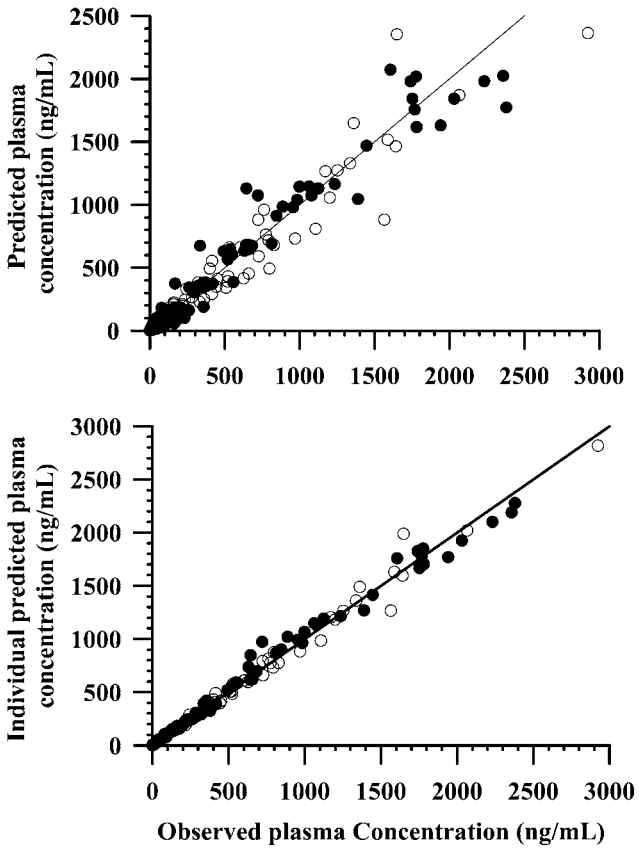

Fig. 4. Scatterplots of individual-predicted (top) and population-predicted (bottom) montelukast concentrations vs. observed concentrations. Solid circles represent values in adults (study 1) and open circles represent values in children aged 6 to 14 years (study 2). The solid line is the line of identity.

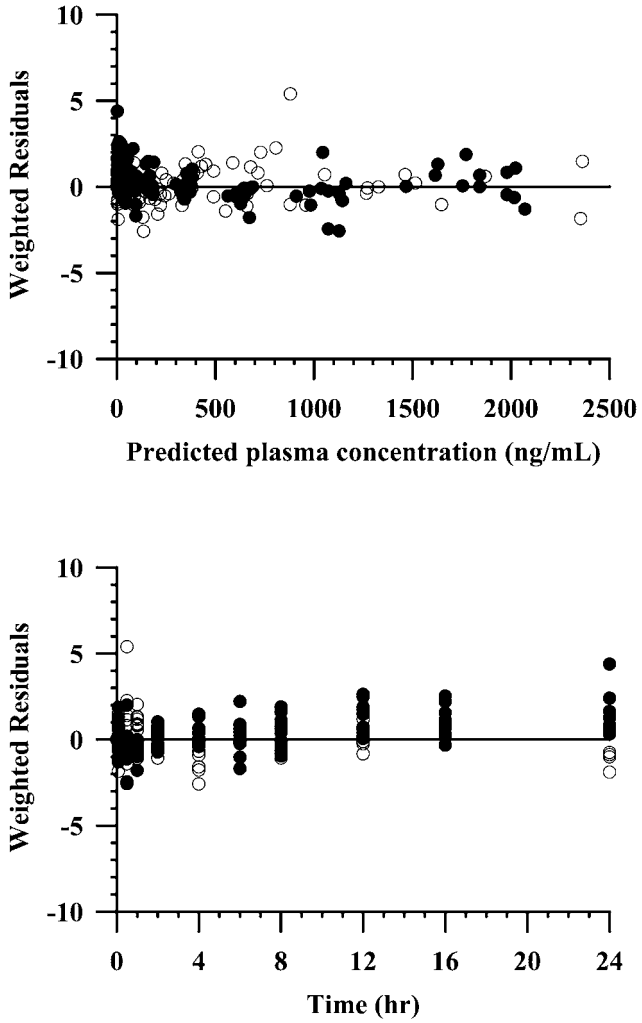

Fig. 5. Scatterplots of weighted residuals vs. predicted montelukast concentrations (top) and time (bottom). Solid circles represent values in adults (study 1), and open circles represent values in children aged 6 to 14 years (study 2).

girls aged 6 to 14 years (22). The design included sampling of 1000 subjects and doses of 3.5, 4.5, and 5.25 mg were tested. The distribution of AUCs (calculated as *dose*/*CL*) after the different doses was investigated.

RESULTS

Results indicate that intravenous montelukast was safe and well tolerated in both the studies. Twenty-five subjects (14 males and 11 females) completed study 1 of which 12 subjects had pharmacokinetic evaluation. Eleven subjects (all males) completed pharmacokinetic evaluation in study 2. The patient demographics for both studies are listed in Table I. Adverse experiences (AE) were few and transient and probably not drug-related. There were no serious AEs. No clinically significant intravenous site irritation was noted.

Population Pharmacokinetic Analysis

Figure 1 is a scatterplot of plasma montelukast concentrations vs. time. The kinetics were clearly multiexponential and so a one-compartment model was not evaluated. There

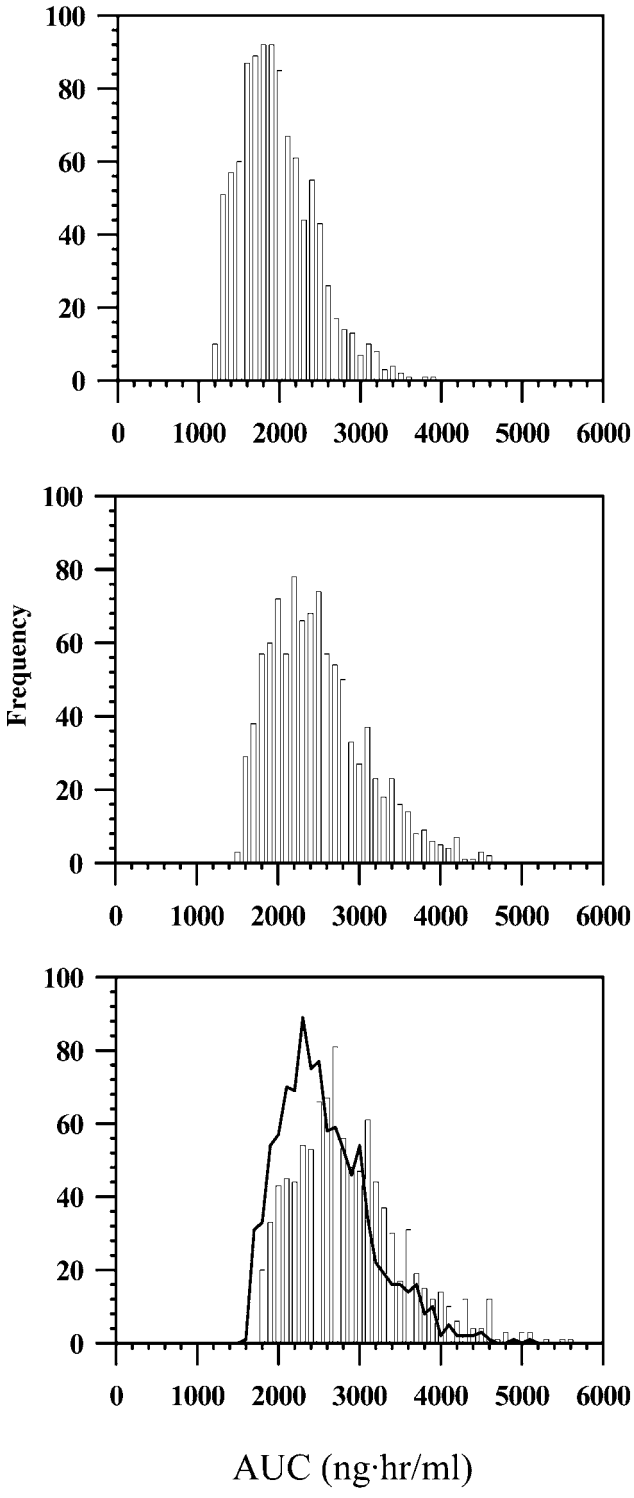

Fig. 6. Histograms showing model predicted distribution of AUCs after single intravenous doses of 3.5 mg (top) and 4.5 mg (middle), and 5.25 mg (bottom) in children aged 6 to 14 years (39.8 ± 15.65 kg). The bottom graph compares the predicted distribution of AUCs after single intravenous montelukast doses of 5.25 mg in children aged 6 to 14 years weighing 39.8 ± 15.65 kg (vertical bars) and 7 mg in adults aged 20 years and above weighing 80.1 ± 29.7 kg (solid line). Simulations were performed by sampling 1000 subjects at the described dose levels using the three-compartment (base 2) model.

Table IV. Model Predicted Exposure Estimates of Montelukast in Adults and Children

Population	Route of administration	Dose (mg)	Mean AUC (ng · h/ml)	AUC range (ng · h/ml)
6–14 years	Intravenous	5.25	2815	1724–5522
6–14 years	Intravenous	4.5	2445	1301–4647
6–14 years	Intravenous	3.5	1924	1135–3850
Adults	Intravenous	7	2521	1590–5052
Adults	Oral	10	2448	2448 ± 779[a]

[a] Observed mean ± standard deviation (source: Ref. 26).

was a significant difference of 71.4 U in the NONMEM OFV, and the AIC value also decreased by 67.4 U with a three-compartment model compared to a two-compartment model. There was a clear improvement in the goodness of fit as well. Based on the OFV and AIC values, plots of weighted residuals and visual inspection of the fittings, a three-compartment linear model (Fig. 2) was chosen to describe the pharmacokinetics of montelukast after intravenous administration. The interindividual variability was estimated on all parameters except V_2, Q_2, and Q_3, as estimates of these were associated with confidence intervals that included zero. A combined additive and proportional error model (OFV = 1580.66) was found to better describe the residual variability than the proportional error model (OFV = 1645.24) or the additive error model (OFV = 1860.803).

Plots of individual empirical Bayes estimates vs. the covariates revealed an influence of both TBW and age on clearance (CL), central volume of distribution (V_1), and peripheral volume of distribution (V_3). The shape of the curve suggested a possible power function. The univariate analysis indicated that both age and TBW lower the OFV significantly when added to each of the structural parameters. The most significant drop in OFV was associated with the addition of TBW on CL (base 1). The power model was associated with a lower OFV compared to the linear model with intercept (1546.689 vs. 1547.908). The stepwise addition of TBW and age on the various model parameters indicated that TBW was always associated with a more significant drop in OFV compared to age. As indicated in Table II, covariate analysis yielded a final model that included effect of TBW on CL and on V_1 (base 2). Again, the power model was associated with a lower OFV compared to the linear model with intercept (1507.844 vs. 1509.615). There appeared to be an effect of TBW on V_3 as well; however, the model was rejected because of insufficient precision. During backward elimination, we attempted to refine the base 2 model by setting the exponent of the power functions to 1. There was a significant increase in the OFV, and hence it was confirmed the power exponents were essential. The covariate relationships for the typical value of the parameters were $TVCL = \theta_{CL} \times (TBW^{\theta 1})$ and $TVV_1 = \theta_{V1} \times (TBW^{\theta 2})$, where θ_{CL}, θ_{V1}, θ_1, and θ_2 are 175, 156, 0.635, and 0.726, respectively. Upon addition of these demographic effects, the interindividual variabilities on CL and V_1 improved from 37% and 37.3% to 24.2% and 14%, respectively. The individual CL and V_1 values along with the population predictions are shown in Fig. 3. Residual variability consisted of a combined additive and proportional error of 3.7 ng/ml and 10.4%, respectively. The population parameter estimates from the final model are indicated in Table III. As shown in Fig. 4, the population and individual predicted concentrations vs. observed concentrations were close to the line of unity. In general, the weighted residuals were uniformly distributed around zero as shown in the goodness of fit plots (Fig. 5). Taken together, these plots indicate that the final model appears to adequately characterize the disposition of montelukast.

Clinical Trial Simulations

Figure 6 shows histograms comparing the predicted distribution of exposures after doses of 3.5, 4.5, and 5.25 mg in children aged 6 to 14 years. Trial simulations indicate that a dose of 5.25 mg in 6- to 14-year-olds appears to best approximate the distribution of AUCs after a 7-mg dose in adults, whereas the 3.5-mg and 4-5-mg doses would lead to underdosing in a fraction of the subjects. Table IV shows the model-predicted mean AUCs and the distribution of AUCs in adults and pediatric subjects after intravenous administration along with previously published results after oral administration in adults. These results indicate that a 7-mg intravenous dose in adults yields mean exposures comparable to those after a 10-mg film-coated tablet in adults. A 5.25-mg intravenous dose in children aged 6 to 14 years can be anticipated to produce higher mean exposures. Because the intravenous formulation is for administration in an emergency setting in pediatrics, it is preferable to be cautious and aim for mean exposures that are well tolerated and slightly higher than those already proven to be efficacious in adults. As shown in Fig. 7, almost all 6- to 14-year-old children in the median weight range (20 to 51 kg) will attain exposures of greater than 2500 ng·h/ml after doses of 5.25 mg. The simulations also suggest that at a 5.25-mg dose, it is likely that a small fraction of the subjects might have exposures as high as 5500 ng·h/ml. However, these exposures do not pose a concern with respect to safety, as early clinical studies have shown that intravenous doses up to 18 mg (mean exposure ~7600 ng·h/ml) have been well tolerated in adults (13). Exposures of 3528 (±1883) ng·h/ml have been observed in pediatric patients after oral administration of a 10-mg dose of the film-coated tablet formulation of montelukast, and these were well tolerated as well (23). Also, it is known that montelukast has a wide therapeutic index, and no dose-related toxicity has been observed in adult subjects treated with oral doses substantially higher than 10 mg (24). Simulations using typical population parameter estimates in adults and children indicate that a 5.25-mg intravenous dose can be generally expected to produce concentrations equal to or higher than those after a 7-mg intravenous dose in adults and would prevent underdosing in children aged 6 to 14 years (Fig. 8).

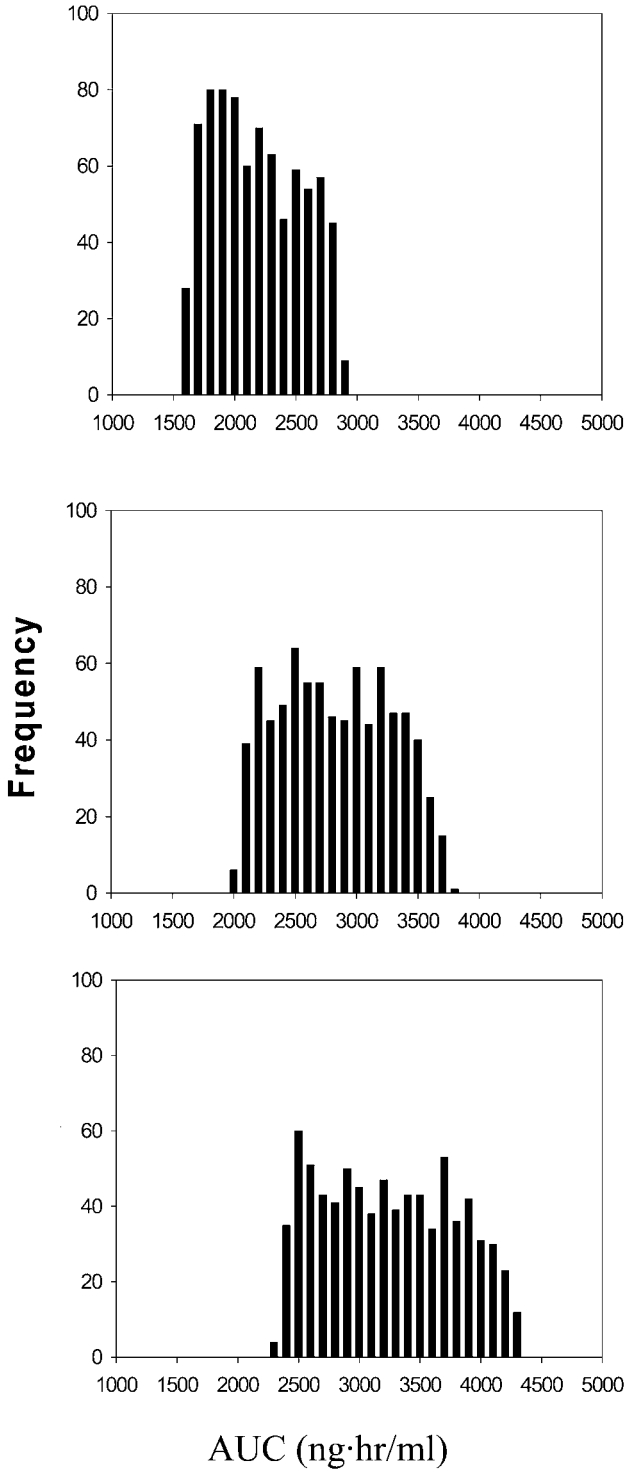

Fig. 7. Histograms showing model predicted distribution of AUCs after single intravenous doses of 3.5 mg (top), 4.5 mg (middle), and 5.25 mg (bottom) of montelukast in children aged 6 to 14 years weighing 20 to 51 kg (corresponding to the 50th percentile weight for age). The trial design included sampling of 1000 subjects at each dose level using the three-compartment (base 2) model.

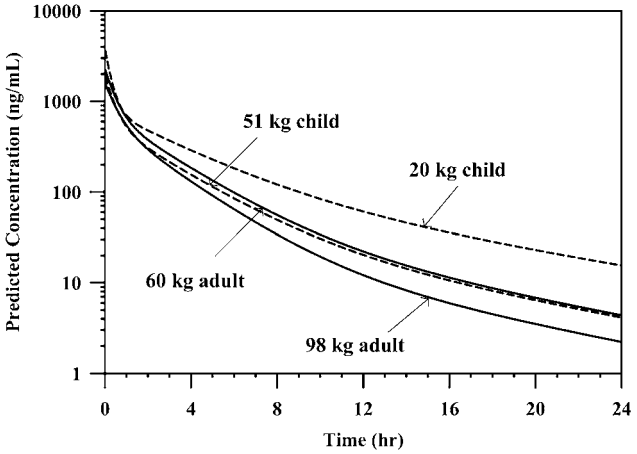

Fig. 8. Population predictions for montelukast plasma concentrations after intravenous administration of montelukast (without inter-individual variability) based on a three-compartment (base 2) model. The solid lines bracket the pharmacokinetic profile for a typical adult weighing between 60 and 98 kg after a 7-mg intravenous dose. The dashed lines bracket the pharmacokinetic profile for a typical child weighing between 20 and 51 kg (corresponds to the 50th percentile of weight in children aged 6 to 14 years)after a 5.25 mg intravenous dose.

DISCUSSION

The pharmacokinetics of montelukast after single-dose oral administration have been extensively studied (11,13, 16,25). Most of the data published include routine noncompartmental analysis. Sparse data from pediatric studies in children aged 6 months to 5 years have been modeled with a one-compartment model (15,16,23); however, the choice of model was empirical, and other models were not explored due to the sparsity of the data collected.

To our knowledge, this is the first report describing the development of a population pharmacokinetic model for montelukast after intravenous administration. The linear three-compartment population PK model developed appears to adequately describe the pharmacokinetics of montelukast after intravenous administration in adults and children. The steady-state volume of distribution and clearance in a 70-kg adult were estimated to be 8.2 L and 43 ml/min, respectively, which is consistent with published results that use traditional noncompartmental analysis (13). Previous studies after oral administration of montelukast have indicated that the pharmacokinetic profiles of montelukast are different in adults and children (23). Consistent with those observations, we observed dissimilar pharmacokinetics after intravenous administration between the two populations that we studied. The clearance and volume of distribution were lower in pediatric patients (6 L and 19.5 ml/min in a 20-kg child). Our model suggests that TBW rather than age is the primary factor contributing to the difference. This is supported by an earlier study where no significant pharmacokinetic differences were found between the young and elderly (12).

What is the best method to include effect of TBW in the population PK model is a matter of debate. Fixing the power exponent to theoretical values based on allometric principles would be one reasonable approach (26,27). We chose to estimate the power exponents because allowing the parameters to vary allowed for an improvement in the fit. Montelukast undergoes extensive metabolism with only a small fraction of the dose being excreted unchanged in the bile. Oxidative metabolism is predominantly catalyzed by CYP3A4 and CYP2C9, and comparative studies with human liver micro-

somes suggest that there are no significant differences in montelukast metabolism between adults (ages 50–65 years) and children (ages 6–11 years) (28). Thus, it is speculated that an increase in the liver enzyme capacity with increasing body weight is probably responsible for the observed increase in clearance with TBW; however, the power exponent of 0.635 does suggest that clearance probably increases proportionally to body surface area. The estimated volume of distribution of the central compartment was similar to the blood volume in humans. Because V_1 increases more rapidly with TBW than CL does, the elimination half-life is predicted to change in a slightly nonlinear manner with TBW; from 0.9 h at 70 kg to 0.8 h at 20 kg. In the final three-compartment pharmacokinetic model, effect of age on CL and V_1 was found not to be significant in the presence of effect of TBW. This is not unexpected, given the association of body weight with age. The association between TBW and the structural parameters resulted in a substantial decrease in interpatient variability (63% for V_1 and 35% for CL), indicating that most of the variability in these parameters can be attributed to differences in TBW. The estimated proportional component agrees with the accuracy and precision of the assay.

Dose-ranging studies for montelukast in adults have established 10 mg per day as the minimal dose to achieve maximal efficacy (24,29,30). A 10-mg film-coated tablet in adults, a 5-mg chewable tablet in children aged 6 to 14 years, and a 4-mg chewable tablet or oral granules in children aged 2 to 5 years are approved for use in the clinic. These oral doses yield similar systemic exposures that are also associated with efficacy in the respective age groups (15,17,23). In adult patients with chronic asthma, a single 7-mg intravenous dose was found to be as effective as a 10-mg oral dose of montelukast (31). As shown in this report, a 7-mg intravenous dose is associated with mean plasma exposures comparable to those following a 10 mg oral dose of montelukast in adults. Dose selection in 6- to 14-year-old children was performed by identifying an intravenous dose with the currently developed model that can be expected to attain levels of exposure comparable to those described above. This pharmacokinetically guided dose selection, using AUC indicates that a 5.25-mg dose would be efficacious for children aged 6 to 14 years. We simulated the population average concentration-time profile at a dose of 5.25 mg based on the mean population parameter estimates, and this analysis confirms the appropriateness of the 5.25-mg dose in the 6- to 14-year-old patient population. Our modeling results suggest that it would be ideal to dose montelukast based on TBW. However, based on the range of exposures expected, and given the wide therapeutic index of montelukast (24,29,30,32), our analysis also indicates that it would be sufficient to identify subpopulations of TBW (corresponding to specified pediatric age groups) and adjust doses accordingly.

In conclusion, we have reported the population pharmacokinetic model building process and the exploration of demographic subpopulations for which dose adjustment is needed. Defining the pharmacokinetic parameters of montelukast allowed for a more precise determination of dosing to accommodate changes associated with physiologic parameters like age and TBW. The appropriateness of the 5.25-mg dose will be tested in future efficacy studies. It should be recognized that the current model is built on a limited data set. Inclusion of data from future studies would be helpful in assessing the validity of the model. During the covariate analysis, there appeared to be a possible slight dependency of V_3 on TBW; additional data would further help in investigation of this effect as well and possible refinement of the model. Nevertheless, the population pharmacokinetic model developed appears to reasonably describe the pharmacokinetics of montelukast after intravenous administration and adds to our knowledge of disposition of this clinically important drug.

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