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Original Article

Population pharmacokinetics of pranlukast hydrate dry syrup in children with bronchial asthma

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Abstract

Background: This is the first report about the pharmacokinetics (PK) of pranlukast in children. The aim of the present study was to assess the PK parameters of pranlukast in children and to compare them with those in adults.

Methods: Six healthy adult male volunteers and 22 children with bronchial asthma at 3–14 years of age were enrolled in the study. Both 225 and 112.5 mg pranlukast hydrate dry syrup was administered orally to adults, whereas 3.5 mg/kg pranlukast hydrate dry syrup was given to children. Blood samples were obtained at approximately 20 time points per adult (n = 121) and at two or three time points per child (n = 54). Population PK analysis was performed using NONMEM (Globomax, Hanover, MD, USA). The concentration–time-course of pranlukast was described by using a one-compartment model with first-order absorption. The robustness of the final model was evaluated using 200 bootstrap samples.

Results: Apparent clearance (CL/F) was 1.81 and 1.14 L/h per kg in children and adults, respectively. According to subgrouping of children, no significant difference was observed in CL/F between infants (3–6 years of age) and schoolchildren (7–14 years of age). The interindividual variability of CL/F accounted for 48.7%. The additive and proportional residual variability was 7.33 ng/mL and 73.8%, respectively. All fixed effect parameters fell within 10% of the bootstrapped mean.

Conclusions: Compared with adults, children showed a higher CL/F and more rapid elimination after ingestion of pranlukast hydrate dry syrup. However, no significant variation was seen in CL/F between infants and schoolchildren.

Key words: children with bronchial asthma, population pharmacokinetics, pranlukast.

Introduction

Pranlukast was developed as a specific receptor antagonist of leukotriene C_4, D_4 and E_4.[1] It has been reported that administration of pranlukast is associated with inhibition of early and late-phase bronchoconstriction,[2–4] airway hyperresponsiveness[4,5] and eosinophil infiltration into airways,[6,7] evolving into effective prevention of exercise-induced asthma.[8] However, there has been no report on the pharmacokinetics of pranlukast in children. This is because a relatively large number of blood samples is required for traditional pharmacokinetic studies, thereby preventing exploration the pharmacokinetics of pranlukast in children due to ethical and practical reasons. However, using the population pharmacokinetic approach, only a few plasma concentration measurements per patient are necessary for adequate analysis of the data. The objective of the

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present study was to estimate the pharmacokinetic parameters of pranlukast in children with bronchial asthma and to compare these parameters with those in healthy adult volunteers.

METHODS

Studies on healthy adult male volunteers (study 1) and on children with asthma (study 2) were conducted according to two different protocols. The study protocols were reviewed and approved by the Institutional Review Boards of each clinical study site. Written informed consent was obtained from all adult subjects in study 1. In study 2, written informed consent was obtained from parents or legal guardians of all children. In addition, informed assent was obtained from children over 8 years of age.

Study 1

In study 1, six healthy males aged between 21 and 36 years participated (Table 1). All subjects received single oral doses of either 225 or 112.5 mg pranlukast. Blood samples were obtained at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 h after drug administration. The total number of data points reached 121. The plasma concentration of pranlukast in adults was determined using high-performance liquid chromatography (HPLC), following the assay procedures stated below. Initially, pranlukast was extracted from plasma with ethanol and the supernatant was evaporated to dryness. The residue was dissolved in 1% tartaric acid solution followed by extraction with ethyl acetate. The organic layer was evaporated to dryness; subsequently, the residue was dissolved in ethanol and ethyl acetate and the resultant solution was then applied to a SEP-PAK Si column (Waters, Milford, MA, USA). After the eluate was evaporated to dryness, the residue was reconstituted with mobile phase and injected into the HPLC system. The linear range of the concentration curve was 10–1000 ng/mL, with the lower limit of quantitation being 10 ng/mL.

Table 1 Demographic characteristics of the subjects

	Study 1 Adults	Study 2 Children
Disease	Healthy	Asthma
Dose	1.125, 2.25 g/person	35 mg/kg
No. subjects	6 (6 M)	22 (14 M, 8 F)
No. time points	121	54
Age (years)*	26.0 (21–36)	6.5 (3–14)
Bodyweight (kg)*	66.6 (55.4–76.3)	24.0 (12.3–53.0)

*Data for age and bodyweight are the average with the range given in parentheses.

Study 2

In study 2, 22 patients with bronchial asthma aged between 3 and 14 years of age were involved (Table 1). There were 11 infants (3–6 years old) and 11 schoolchildren (7–14 years old). Pranlukast hydrate dry syrup was administered orally twice a day at 3.5 mg/kg. The blood sampling was conducted at two time points: from 4 to 6 h and from 8 to 10 h after drug administration. If possible, a third sampling was performed from 1 to 3 h after administration. In total, 54 data points were used. The plasma concentration of pranlukast was determined by liquid chromatography connected to a tandem mass spectrometer (LC/MS/MS). Pranlukast was extracted from plasma by liquid–liquid extraction with 0.3 mol/L potassium dihydrogen phosphate solution and ethyl acetate and the organic layer was then evaporated to dryness. The residue was dissolved in mobile phase and was then injected into the LC/MS/MS system. The linear range of the concentration curve was 2–200 ng/mL, with the lower limit of quantitation being 2 ng/mL. Cross-validation demonstrated that HPLC and LC/MS/MS generated equivalent results.

Data analysis

Using the NONMEM program (double-precision NONMEM Ver. V level 1.1; Globomax, Hanover, MD, USA), estimates were obtained for the population means of pharmacokinetic parameters, interindividual variability in these parameters and residual variability between the observed and predicted concentrations of pranlukast hydrate. The concentration–time-course of pranlukast was presented using a one-compartment model with first-order absorption and elimination. The pharmacokinetics of pranlukast were described by the following equation:

$$C_{ij} = \frac{Ka_i \bullet D_i}{Vd/F_i \bullet (Ka_i - CL_i/Vd)} \times \left(\exp\left(-\frac{CL_i}{Vd} \bullet (t_{ij} - t_{lagj})\right) - \exp\left(-Ka_i \bullet (t_{ij} - t_{lagj})\right)\right) \quad [1]$$

where Cij is the plasma concentration measured in the jth subject at the ith time point (t_{ij}), D_i, CL_i, and Ka_i are the dose, total body clearance and first-order absorption

rate constant in the jth subject, respectively, and Vd/F_j, F_j and t_{lagj} are an apparent volume of distribution, bioavailability after oral administration, and lag time of absorption, respectively.

The interindividual variabilities in pharmacokinetic parameters were modeled with proportional error according to the following equation:

$$P_j = \tilde{P}j\,(1 + \eta_j) \quad [2]$$

where P_j is the parmacokinetic parameter for jth individual, $\tilde{P}_j$ is the jth individual parameter with the regression model and ηj is an independently distributed random variable with a mean of zero and variance ω^2.

The intrasubject residual variability was also modelled with the combination of additive and proportional error models according to the following equation:

$$C_{ij} = \tilde{C}_{ij}\,(1 + \varepsilon_{1ij}) + \varepsilon_{2ij} \quad [3]$$

where C_{ij} is the ith measured plasma concentration in the jth subject, $\tilde{C}_{ij}$ is the corresponding predicted plasma concentration and ε_{1ij} and ε_{2ij} are residual variability terms, representing independent identically distributed statistical errors with a mean of zero and variance σ^2. The model for the residual variability was determined from preliminary analysis.

To test the significance of various factors affecting the pharmacokinetic parameters, we used the value of objective function determined in the NONMEM fitting routine. The difference in objective function values obtained by comparing each model is asymptotically distributed as Chi-squared with degree of freedom equal to the difference in the number of parameters between the two models. To identify potentially significant factors, the difference in the objective function associated with $P < 0.05$ was required.

The accuracy and robustness of the final model were assessed by using a bootstrap method.[9–11] Two hundred data sets were reconstructed by resampling six adults and 22 children from the original data. The mean parameter estimates obtained from 200 bootstrap replications were compared with those obtained from the original dataset.

The dose of pranlukast was 7 mg/kg per day twice a day in children, which was approximately the same for adults (450 mg/day) in terms of dose per bodyweight. Accordingly, the dose administered for children and the results obtained from the population analysis permitted us to simulate the concentration–time profile for both adults and children.

RESULTS

The plasma concentrations of pranlukast used for the population pharmacokinetic analysis are shown in Fig. 1. The basic model was tested initially with age as a covariate. Model 2 presenting the difference of apparent clearance (CL/F) between all children (< 15 years of age) and adults produced a significant improvement in the fit of the model to the data. A further improvement was not observed when the difference in CL/F of the subgroups, namely between infants (3–6 years) and schoolchildren (7–14 years) was included in the model. Therefore, Model 2 was selected as the basic model in the present study. All results are given in Table 2.

At the model-building stage, the following clinical factors were tested individually as covariates: gender, concomitant medication of theophylline, total bilirubin, lactate dehydrogenase and serum creatinine. However, no clinical factors were found to influence CL/F. These results are shown in Table 3.

The parameter estimates of the final regression model are shown in Table 4. The final regression model is presented below:

CL/F (L/h per kg) = 1.14×1.59^{GE}
Apparent distribution volume (Vd/F; L/kg) = 1.53
Absorption rate constant (Ka; /h) = 0.493
Lag time of absorption (t_{lag}; h) = 0.981
with GE = 1 for children and 0 for adults.

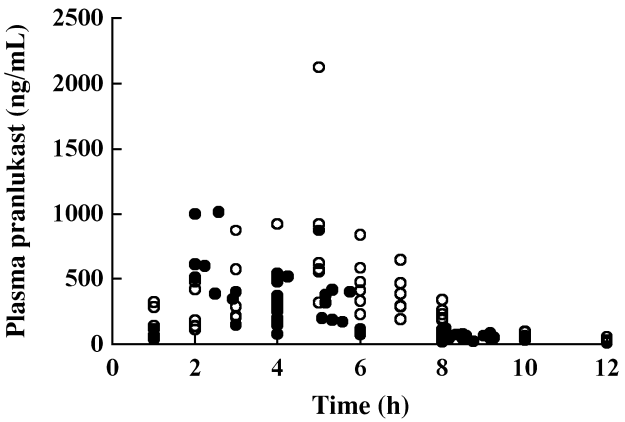

Fig. 1 Time after administration versus plasma concentrations of pranlukast in six adults receiving 225 mg pranlukast (○) and in 22 children receiving 3.5 mg/kg (●).

Table 2 Determination of the basic model (effect of age on apparent clearance)

Model	Equation	LLD	*P*
1. Simple model	$CL/F = \theta_1$ $Vd/F = \theta_2$ $Ka = \theta_3$ $t_{lag} = \theta_4$		
2. Does the group 'children' influence CL/F?*	$CL/F = \theta_1 \times \theta_5^{GE}$ $Vd/F = \theta_2$ $Ka = \theta_3$ $t_{lag} = \theta_4$	25.020	< 0.05
3. Does the age of children influence CL/F?†	$CL/F = \theta_1 \times FAC1 \times FAC2$ $Vd/F = \theta_2$ $Ka = \theta_3$ $t_{lag} = \theta_4$	2.891	NS

*GE for children = 1; GE for adults = 0.

†FAC1 is set to θ_5 if the patient is an infant (3–6 years old) and to 1 otherwise; FAC2 is set to θ_6 if the patient is a schoolchild (7–14 years old) and to 1 otherwise.

CL/F, apparent clearance; Vd/F, apparent distribution volume; Ka, absorption rate constant; t_{lag}, lag time of absorption.

Table 3 Effect of individual covariates on apparent clearance

	Equation	θ_5	θ_6	LLD	*P*
Basic model	$CL/F = \theta_1 \times \theta_5^{GE}$ $Vd/F = \theta_2$ $Ka = \theta_3$ $t_{lag} = \theta_4$	1.59			
GEND	$\theta_1 \times \theta_5^{GE} \times \theta_6^{GEND}$	1.56	1.13	0.775	NS
THEO	$\theta_1 \times \theta_5^{GE} \times \theta_6^{THEO}$	1.85	0.828	1.568	NS
TBIL	$\theta_1 \times \theta_5^{GE} \times \theta_6^{TBIL}$	1.57	1.11	0.325	NS
LDH	$\theta_1 \times \theta_5^{GE} \times \theta_6^{LDH}$	1.53	1.11	1.915	NS
CRE	$\theta_1 \times \theta_5^{GE} \times \theta_6^{CRE}$	1.31	1.23	1.320	NS

GEND was designated 0 in males, and 1 in females; THEO was designated 0 in the case of non-coadministration of theophylline and 1 in the case of coadministration.

TBIL, total bilirubin; LDH, lactate dehydrogenase; CRE, serum creatinine. These were designated 0 in the case of normal values and 1 in the case of abnormal values.

CL/F, apparent clearance; Vd/F, apparent distribution volume; Ka, absorption rate constant; t_{lag}, lag time of absorption.

The interindividual variabilities in CL/F, Ka and t_{lag} were 48.7, 21.6 and 15.7%, respectively. The additive and proportional residual variabilities accounted for 7.33 ng/mL and 73.8%, respectively. The relationship between observed and predicted values obtained by Bayesian estimation is illustrted in Fig. 2.

The parameter estimates of the final model and the results of the bootstrap validation step are listed in Table 5. All structural parameters (θ) were within 10% of the bootstrapped mean, whereas the variance parameters (ω, σ), except for ω_2, also fell within 10% of the bootstrapped mean.

Figure 3 illustrates the mean concentration–time profiles for pranlukast in adults and children predicted from the final population pharmacokinetic model.

Discussion

The objective of the present study was to characterize the pharmacokinetics of pranlukast in children by using numerical analysis methodology for sparse data. In pharmacokinetic analysis, the population approach provides an advantage by permitting us to extract pharmacokinetic information from sparse or fragmented data,

further evolving into our successful assessment of factors that may influence drug disposition.

The population pharmacokinetic analysis was conducted by comparing a subgroup consisting of infants from 3 to 6 years of age with another subgroup comprising schoolchildren aged from 7 to 14 years. Age was treated as a discrete variable, because 22 cases were too few in number to be treated as a continuous function. In the present analysis, no significant difference was observed for CL/F between the two subgroups of infants and schoolchildren. In contrast, a difference in CL/F was observed between all children and adults. The CL/F in the children was 1.59-fold higher than that in adults, indicating that pranlukast hydrate was eliminated more rapidly in children than in adults.

It is known that clearance per bodyweight decreases in parallel with the growth of children following medication for several types of drugs, such as ketotifen,[12]

Table 4 Parameters estimated with the final model

	Estimates
$CL/F = \theta_1 \times \theta_5^{GE}$	
θ_1	1.14 (0.47–1.81)
θ_5	1.59 (1.06–2.12)
$\omega_{CL/\Phi}$ (%)	48.7
$Vd/F = \theta_2$	
θ_2	1.53 (0.63–2.43)
$\omega_{Vd/F}$ (%)	Fixed
$Ka = \theta_3$	
θ_3	0.493 (0.357–0.629)
ω_{Ka} (%)	21.6
$t_{lag} = \theta_4$	
θ_4	0.981 (0.960–1.002)
ω_{tlag} (%)	15.7
Residual variability	
Proportional, σ_1 (%)	73.8
Additive, σ_2 (ng/mL)	7.33

Estimates are given as the mean with 95% confidence intervals in parentheses.

CL/F, apparent clearance; Vd/F, apparent distribution volume; Ka, absorption rate constant; t_{lag}, lag time of absorption.

The CL/F of adults: $\theta_1 = 1.14$; CL/F of children: $\theta_1 \times \theta_5 = 1.81$.

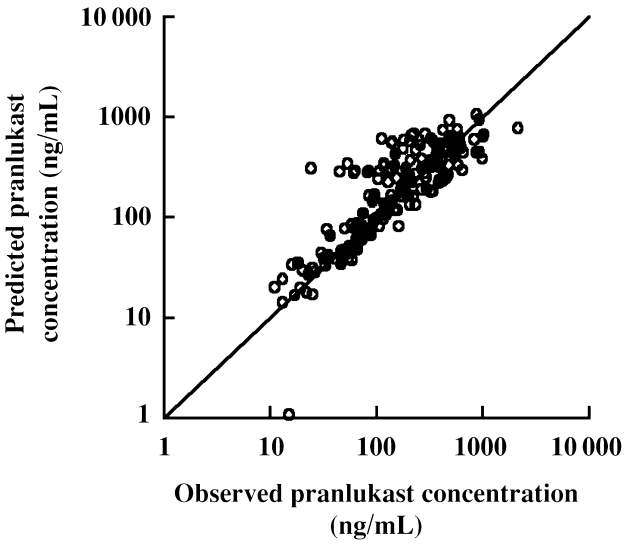

Fig. 2 Observed versus predicted concentrations of pranlukast from a Bayesian post hoc analysis of the final model with 121 time points obtained from six adults (○) and 54 time points obtained from 22 children (●).

Table 5 Results of Bootstrap validation

Parameter	Final model*	Bootstrap†	Difference (%)‡
θ_1	1.14 (0.34)	1.07 (0.16)	–6.4
θ_2	1.53 (0.46)	1.51 (0.41)	–1.2
θ_3	0.493 (0.069)	0.536 (0.098)	8.8
θ_4	0.981 (0.011)	0.982 (0.009)	0.1
θ_5	1.59 (0.27)	1.66 (0.31)	4.2
$\omega_{CL/F}$ (%)	48.7	47.5 (39.2)	–2.4
ω_{Ka} (%)	21.6	39.1 (49.9)	81
ω_{tlag} (%)	15.7	14.5 (10.2)	–7.7
σ_1 (%)	73.8	72.5 (41.1)	–1.7
σ_2 (ng/mL)	7.33	7.55 (4.80)	3.0

Data show the mean with SEM given in parentheses.

*Obtained from the original dataset.

†Calculated from 200 bootstrap replicates.

‡(Bootstrap value-final model value)/final model value 100%.

CL/F, apparent clearance; Vd/F, apparent distribution volume; Ka, absorption rate constant; t_{lag}, lag time of absorption.

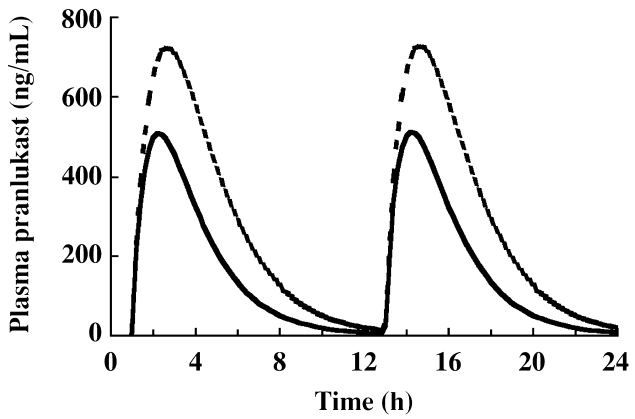

Fig. 3 Simulation curve of pranlukast concentration in plasma after oral administration of pranlukast hydrate dry syrup at 3.5 mg/kg to adults (-----) and children (——) twice a day.

phenobarbital[13] and valproric acid;[14] this phenomenon is likely to be attributed to the higher liver weight relative to bodyweight in children than in adults.[15] Accordingly, it is postulated that medication with drugs susceptible to predominant metabolism in the liver demonstrates higher CL/F in children than in adults. Pranlukast is considered to be mainly metabolized in the liver because little pranlukast hydrate is excreted into the urine. Hence, the present results are consistent with previous findings.

A possible interaction of pranlukast following concomitant use of theophylline, which is frequently used for the treatment of bronchial asthma, was investigated in the present study. However, theophylline did not appear to influence the CL/F of pranlukast.

The mean parameter estimates obtained with the 200 bootstrap replicates of the data were within 10% of those obtained from the original data, except for the inter-individual variation of Ka. This may be due to insufficient data during the absorption phase. This final pharmacokinetic model was useful for the prediction of CL/F.

In conclusion, pranlukast hydrate showed a higher CL/F and was eliminated more rapidly in children than in adults. However no significant variation was observed for CL/F in two child subgroups, namely between infants (3–6 years) and schoolchildren (7–14 years).

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