Population pharmacokinetic analysis of cefditoren pivoxil in pediatric patients with infection

Kayoko Matsumoto, Nobuo Sato, Nayu Mitomi and Shigeki Shibasaki

Pharmaceutical Research Center, Meiji Seika Pharma Co., Ltd.

(Received for publication October 2, 2013)

Population pharmacokinetic analysis was conducted on cefditoren pivoxil (CDTR-PI, Brand name: MEIACT, Meiji Seika Pharma Co., Ltd.), a third generation oral antibiotic, using plasma concentrations of cefditoren (CDTR, total number of sampling points: 578) obtained from pediatric patients (153 subjects, dose: 5.62± 1.62 mg/kg) after CDTR-PI administration as well as demographic data of those subjects. NONMEM (Ver. VI LEVEL 2.0) was used as software. The first-order conditional estimation (FOCE) method without interaction was employed as algorithm. A one-compartment model with first-order absorption was used as a pharmacokinetic model. As the result of analysis, the following population pharmacokinetic parameters were obtained for CDTR.

Population mean parameters: ka (hr^{-1})＝0.527, CL/F (L/hr/kg)＝−0.474×Scr ＋0.82, Vd/F (L/kg)＝0.77, Tlag (hr)＝0.282×(1＋0.435×NAT) (NAT: 0＝ Japan, 1＝USA, interindividual variability: ω (ka)＝17.23%, ω (CL/F)＝33.02%, ω (Vd/F)＝86.66%, intraindividual residual variability: σ＝0.428 μg/mL.

Bayes estimation was carried out for each subject using the final model to calculate secondary parameters such as C_{max}, T_{max}, AUC, and $t_{1/2}$. C_{max} and AUC increased significantly with dose. However, T_{max} was approximately 2 hours and $t_{1/2}$ was approximately 1 hour at any dose level, showing no significant dose-dependent changes. When CDTR-PI was administered orally to a child, a significant increase was noted in plasma CDTR concentrations, suggesting high efficacy. In addition, pharmacokinetics of CDTR were simulated in patients with renal impairment using the final model. As a result, a delay in T_{max} and increases in AUC, C_{max}, and $t_{1/2}$ were presumed with increased Scr, and the degrees of such increases were also quantitatively estimated.

As mentioned above, the population pharmacokinetic parameters of CDTR were obtained, which is sure contribute to simulation of its plasma concentrations in patients with various backgrounds and to speculation of its efficacy and safety.

Introduction

Cefditoren pivoxil (CDTR-PI) is a third generation cephalosporin antibiotic synthesized by Meiji Seika Pharma Co., Ltd[1]. It is an oral pro-drug whose gastrointestinal absorption has been enhanced by introducing a pivaloyloxymethyl ester at the C4-carboxylic acid of cefditoren (CDTR) that has a broad spectrum and strong antibacterial activity against aerobic and anaerobic Gram-positive bacteria as well as Gram-negative bacteria[2,3]. After oral administration, this compound is absorbed from the gastrointestinal tract and its ester bond is immediately hydrolyzed by an esterase in the enteric canal walls. It is distributed in plasma and tissues as CDTR, an antibacterial active form[1,4~7]. In Japan, CDTR-PI received manufacturing approval in tablet form for adults and granule form for children in April 1, 1994. The dosing regimen for a child is oral administration of 3 mg/kg after meal per dose, 3 times daily (*t.i.d.*). This compound has been widely used for various types of pediatric infectious diseases, and its efficacy and safety have already been established. As of March 2012, this compound has been approved and marketed for pediatric indication in Korea, Thailand and Turkey, and the same dosing regimen as in Japan is employed in these countries. In recent years, however, a lot of drug-resistant strains has been found against existing oral antibiotics in *Streptococcus pneumoniae* (*S. pneumoniae*) and *Haemophilus influenzae* (*H. influenzae*), the major pathogens for acute otitis media, acute rhinosinusitis, and pneumonia. These diseases become refractory and protracted, which pose a big challenge to antibacterial therapy. To overcome this challenge, a high dose treatment with CDTR-PI has been promoted for CDTR to exert sufficient efficacy. After clinical trials in children to confirm the efficacy, safety, and plasma CDTR concentrations in CDTR-PI administration at 6 mg/kg, *t.i.d.*, dosage up to 6 mg/kg, *t.i.d.* was approved in Japan in 2012.

On the basis of above-mentioned background, thorough investigation of the pharmacokinetic information of this compound in pediatric patients is considered to be useful for speculating the efficacy and safety in patients with different demographic data and dosing regimen. On the other hand, only a few reports are available resulting from clinical pharmacology studies on the pharmacokinetics of this compound in pediatric patients. Therefore, population pharmacokinetic analysis has significant importance. In this study, population pharmacokinetic analysis was conducted on CDTR-PI using plasma CDTR concentrations (153 subjects, 578 sampling points) and the demographic data of pediatric patients enrolled in clinical trials that were conducted in Japan and the USA. For oral administration of CDTR-PI to pediatric patients, population mean parameters of CDTR, interindividual variability, and intraindividual residual variability, were obtained which contributs to simulating its plasma concentrations in patients with various types of backgrounds and speculating its efficacy and safety.

Materials and Methods

Pharmacokinetic sampling

Plasma CDTR concentrations (total sampling points: 578) obtained from 153 subjects (age: 28 days ～11 years and 10 months) in 3 clinical trials that were conducted in Japan between 1991 and 2011[8～10] and 1 clinical trial in the USA between 2000 and 2001, and demographic data of those subjects were used for analysis (Table 1). These trials were all performed according to the declaration of Helsinki, and CDTR-PI administration and blood sampling were conducted after respective attending doctors received parental consent for all subjects. CDTR-PI was administered at doses of 3 mg/kg～6 mg/kg (Japan) or 3 mg/kg～9 mg/kg (USA). Plasma CDTR concentrations were measured with Bioassay method where *Escherichia coli* NIHJ JC-2 was used as a test bacterial strain (quantitation limit: 25 ng/mL, accuracy of determination C.V.: 6～9%[11]), HPLC method (quantitation limit: 250 ng/mL, accuracy of determination C.V.: 3～6%[12～14]), or LC-MS/MS method (quantitation limit: 20 ng/mL, accuracy of determination C.V.: 3.3～16.7%). The plasma concentrations of CDTR and demographic data of the patients used for analysis were collected retrospectively from medical records and clinical study reports.

Table 1. Sources of plasma cefditoren concentration data collected in adult clinical trials

Trial type	Location	Year	Dose (mg/kg)	Sample collection[1] (hr)	Assay	LLOQ[2] (ng/mL)
Phase I Study	Japan	1991-1992	3-6	0.5, 1, 2, 4, 6, 8	Bioassay / HPLC	25 / 250
Phase III Study		2007-2008		1 or 2 points around the C_{max}	LC-MS/MS	20
		2010-2011		1.25, 2		
Phase I Study	USA	2000-2001	3-9	0.5, 1, 1.5, 2, 3, 4, 6, 8		

1) after administration, 2) Lower Limit of Quantification

Software and algorithms

For standard pharmacokinetic analysis, Phenix Winnonlin (ver. 6.1) was used. For population pharmacokinetic analysis, the non-linear mixed effects modeling program, NONMEM (Ver. VI, LEVEL 2.0, PREDPP Ver. V LEVEL 2.0) and Wings for NONMEM (Ver. 6) were used. The first-order conditional estimation (FOCE) method without interaction was employed as algorithm. Digital Visual Fortran (Version 11.1, Intel Corporation) was used as compiler. Wings for NONMEM (Ver. 6) was used for model validation by bootstrap method, and Microsoft Excel 2003 (Microsoft Corporation) was used for preparation of tables and figures as well as calculation of statistical parameters. The computer used for analysis was NEC MC-7 (CPU, Celeron 1.8 GHz; memory, 960 MB; OS, Windows XP Professional).

Population pharmacokinetic analysis

Population pharmacokinetic analysis was conducted using NONMEM to estimate the population pharmacokinetic parameters (population mean parameters, interindividual variability, and intraindividual residual variability).

A one-compartment model with first-order absorption was used for pharmacokinetic modeling (equation shown below). Pharmacokinetic parameters included in the model were absorption rate constant (ka), total clearance adjusted by bioavailability (CL/F), volume of distribution adjusted by bioavailability (Vd/F), and lag time (Tlag). As dose was determined per body weight (mg/kg), the parameters CL/F and Vd/F were assumed to be proportional to body weight.

$$C(t)=ka*Dose/(Vd/F)/(ka-kel)*\{EXP(-kel*(t-Tlag))-EXP(-ka*(t-Tlag))\}$$

C(t): plasma CDTR concentration (μg/mL) at t-hour after CDTR-PI administration
Dose: single dosage (mg/kg)
ka: absorption rate constant (hr^{-1})
F: bioavailability
Vd/F: volume of distribution adjusted by F (L/kg)
kel (=(CL/F) / (Vd/F)): elimination rate constant (hr^{-1})
CL/F: total clearance adjusted by F (L/hr/kg)
Tlag: lag time for absorption (hr)

The exponential error model was used for determination of interindividual variability in pharmacokinetic parameters, and the proportional error model was used for determination of intraindividual residual variability.

Interindividual variability: $P_i=\overline{P}\times Exp(\eta_i)$

Intraindividual residual variability: $Cp_{ij}=\overline{Cp}_{ij}+\varepsilon_{ij}$

P_i: individual pharmacokinetic parameter
$\overline{P}$: population mean of pharmacokinetic parameter
Cp_{ij}: individual plasma concentration
$\overline{Cp}_{ij}$: estimated plasma concentration
η_i: error of interindividual variability in pharmacokinetic parameter (the normally distributed interindividual random effect of mean 0 and variance ω^2)
ε_{ij}: error of intraindividual residual variability in plasma concentrations (the normally distributed intraindividual random effect of mean 0 and variance σ^2)

Firstly, population pharmacokinetic analysis was conducted using the basic model without any covariates. Bayesian method was used to estimate pharmacokinetic parameters for each sub-

ject, and then individual pharmacokinetic parameters and the demographic data of subjects (covariates) were plotted to investigate for any correlations between the parameters.

Covariate analysis

The influence of each subject covariate on the pharmacokinetic parameters was analyzed. The following steps were taken to establish a full model.

Step 1: Demographic data (age, weight: WT, serum creatinine: Scr) were sequentially related to the pharmacokinetic parameters in the basic model (ka, CL/F, Vd/F, T lag) to build additive models. A likelihood ratio test was conducted to assess the significance of decrease in OBJ (ΔObjective function value, OBJ) in this model compared to that in the basic model.

The criteria for judging the significance of ΔOBJ was set to be a significance level of 0.05 or lower in accordance with X^2 distribution. The model with the largest ΔOBJ was selected among significant models.

This procedure was repeated until no more covariates could be included.

Step 2: Using the model selected in Step 1 by incorporating the demographic data, the effect of the gender and the location where the clinical trial was conducted (Japan or the USA) was examined with the likelihood ratio test to build a full model.

Next, a reduced model was built by eliminating fixed effect parameters (THETA) one by one from the full model, and by conducting a likelihood ratio test on the significance of increase in ΔOBJ in this model compared to that in the full model. All insignificant THETAs were removed from the full model for optimization to the final model.

The population pharmacokinetic parameters were estimated using the final model established in the above.

Model evaluation

The validity of the final model was evaluated on the basis of the validity of goodness-of-fit plots shown below:

- —Correlation between predicted concentrations based on population mean parameters (C_{pred_mean}) and observed concentrations in plasma (C_{obs})
- —Correlation between predicted concentrations based on Bayes estimates (C_{pred_indiv}) and observed concentrations in plasma (C_{obs})
- —Distribution of predicted concentrations based on population mean parameters (C_{pred_mean}) and conditional weighted residuals (CWRES)

Bootstap validation was used to evaluate the validity and robustness of the final model. Two hundred data sets were reconstructed by resampling from the original dataset. Successful estimation was defined as the normal completion of both estimation and covariance steps of NONMEM. For each parameter estimate when calculation was finalized without error, the mean, standard

error (SE), minimum value (Min), median value (Median), maximum value (Max), and 95% two-sided confidence interval (CI) in percentage were calculated to examine their similarity to the parameter estimates in the final model.

Calculation of secondary parameters by the Bayesian method

For all patients subjected to analysis, individual secondary parameters based on the Bayesian method were estimated in the final model.

T_{max}＝Tlag＋LN(ka/kel)/(ka－kel)
C_{max}＝ka*Dose/(Vd/F)/(ka－kel)*{EXP(－kel*(T_{max}－Tlag))－EXP(－ka*(T_{max}－Tlag))}
$AUC_{0-\infty}$＝Dose/(CL/F)
$t_{1/2}$＝0.693/kel

Tukey's test was carried out to determine whether there was a significant difference in the secondary parameters for each dose group (3, 5, 6, 7, 9 mg/kg).

Simulation of pharmacokinetic parameters in case of impaired renal function

For pediatric patients with impaired renal function with elevated Scr, the pharmacokinetic parameters of CDTR-PI, and the plasma concentrations were simulated. The dose was set to be 3 mg/kg. Following the guideline for chronic renal diseases[15], Scr was calculated on the basis of Schwartz's conversion formula (shown below) for mild renal impairment (GFR＝70 mL/min/1.73 m^3) or moderate renal impairment (GFR＝40 mL/min/1.73 m^3).

GFR＝k×HT (cm)/Scr (mg/dL) …[18]
GFR: estimated glomerular filtration rate in a child (mL/min/1.73 m^3)
k: coefficient (2～12 years old＝0.55)
HT: height (cm)
Scr: serum creatinine concentration (mg/dL)

2.5 and 6 years old boys with national average heights[16,17] were hypothesized for the simulation.

The following 4 conditions (I～IV) were used for simulation and the results were compared to population mean values:

I. 2.5 years old, male, height 90 cm, mild renal impairment, Scr 0.7 mg/dL
II. 6 years old, male, height 116.5 cm, mild renal impairment, Scr 0.9 mg/dL
III. 2.5 years old, male, height 90 cm, moderate renal impairment, Scr 1.2 mg/dL
IV. 6 years old, male, height 116.5 cm, moderate renal impairment, Scr 1.6 mg/dL

Results

Demographic data

The demographic data of the patients used for analysis are shown in Table 2, and the relationship among them are shown in Fig. 1. The data for analysis included gender, age (years), body weight (WT; kg), serum creatinine concentration (Scr; mg/dL) before the start of administration, and the country where a clinical trial was conducted (Japan or the USA). As for clinical trials conducted in Japan, the subjects were all Japanese. On the other hand, as for clinical trial conducted in the USA, the subjects included Blacks, Caucasians, and Hispanics. The total number of subjects enrolled were 153, among which 108 subjects were from studies conducted in Japan (all administered with the tablet form) and 45 subjects from the study conducted in the USA (all administered with the suspension). When categorized by gender, there were 85 boys and 68 girls. The average dose was 5.62±1.62 mg/kg (mean±S.D.), and the minimum, median and maximum doses were 2.91, 6.00, and 9.18 mg/kg, respectively. WT and Scr tended to increase with age. There was no definite relationships between gender and patients' demographic data (Fig. 1).

Table 2. Summary of patients used in the analysis

A

		Mean ± S.D.	Minimum	Median	Maximum
Total	Dose(mg/kg)	5.62 ± 1.62	2.91	6.00	9.18
(n=153)	Age (year)	4.61 ± 2.88	0.08	4.42	11.80
	WT (kg)	18.00 ± 8.70	3.85	16.00	57.90
	Scr (mg/dL)	0.38 ± 0.14	0.10	0.37	0.90

Gender : male; n=85, female; n=68

B

		Mean ± S.D.	Minimum	Median	Maximum
Japan	Dose(mg/kg)	5.57 ± 1.11	2.98	6.00	6.96
(n=108)	Age (year)	4.43 ± 2.62	0.08	4.25	11.80
	WT (kg)	16.68 ± 6.10	3.85	15.85	37.00
	Scr (mg/dL)	0.38 ± 0.14	0.16	0.34	0.90

Gender : male; n=59, female; n=49

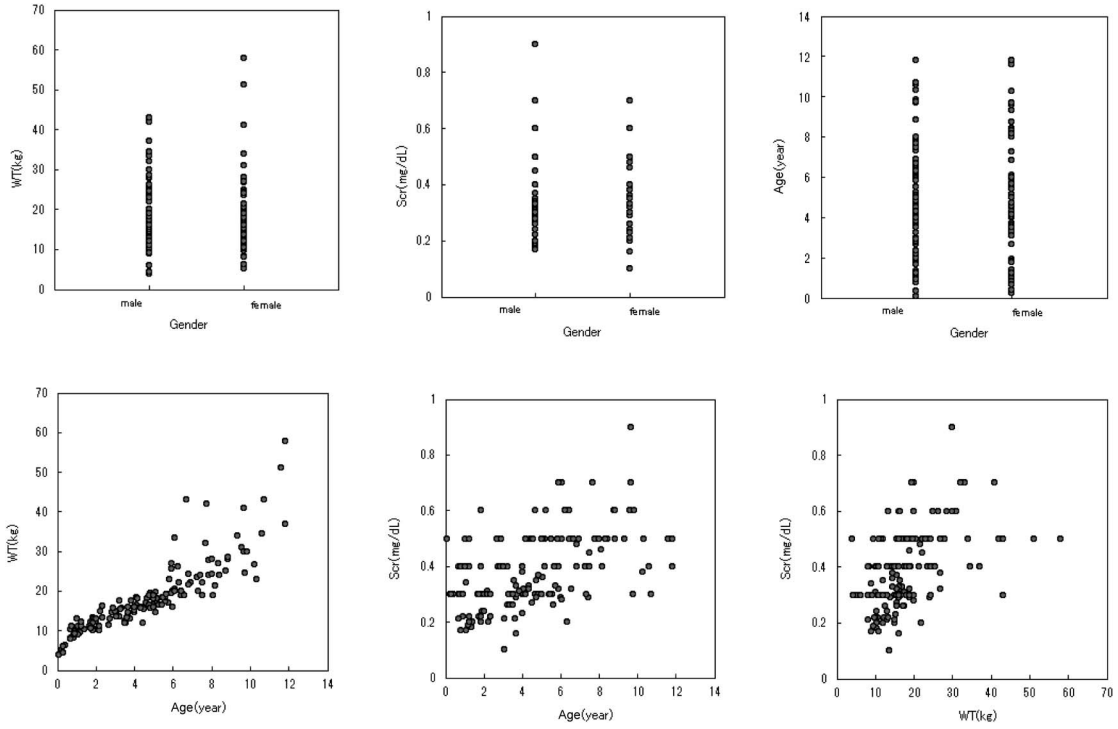
C

		Mean ± S.D.	Minimum	Median	Maximum
USA	Dose(mg/kg)	5.75 ± 2.46	2.91	6.00	9.18
(n=45)	Age (year)	5.03 ± 3.40	0.25	5.00	11.80
	WT (kg)	21.17 ± 12.51	4.40	18.10	57.90
	Scr (mg/dL)	0.40 ± 0.13	0.10	0.40	0.70

Gender : male; n=26, female; n=19

A: demographic data of total subjects (n=153)
B: demographic data of the subjects in Japan (n=108)
C: demographic data of the subjects in USA (n=45)

Fig. 1. Relationships in patient demographic data



Plasma concentrations of CDTR and pharmacokinetic model

The plasma concentrations of CDTR measured in all the clinical trials are shown in Fig. 2. From the results, it was found that CDTR was eliminated mono-exponentially from the plasma. In addition, the concentration-time profiles of plasma concentrations originating from subjects with at least 4 blood samples were individually analyzed by subject using a one-compartment model with first-order absorption with and without lag time. As a result, the AIC (Akaike's information criteria) obtained in the model with lag time was significantly lower than that in the model without lag time (data not shown). Therefore, a one-compartment model with first-order absorption and lag time was used for population analysis of CDTR-PI. The number of samples obtained from one subject in all the clinical trials is shown in Table 3. The most frequently obtained sample size was 8 points per subject; however, sparse data with only 1 point per subject were also included in the analysis.

Population pharmacokinetic analysis

Population mean parameters obtained in the basic model were as follows: ka(hr^{-1})＝0.810, CL/F (L/hr/kg)＝0.639, Vd/F(L/kg)＝1.190, Tlag(hr)＝0.373, interindividual variability：ω(ka)＝82.2%, ω(CL/F)＝39.4%, ω(Vd/F)＝28.7%, intraindividual residual variability：σ＝0.439μg/mL. Interindividual variability for Tlag was not estimated.

Fig. 2. Plasma concentrations of cefditoren after oral administration of cefditoren pivoxil in pediatric patients (153 subjects, 578 points)

Dose: 5.62±1.62 mg/kg (Mean±S.D., 2.91~9.18 mg/kg)
A: Vertical axis: linear, B: Vertical axis: logarithm

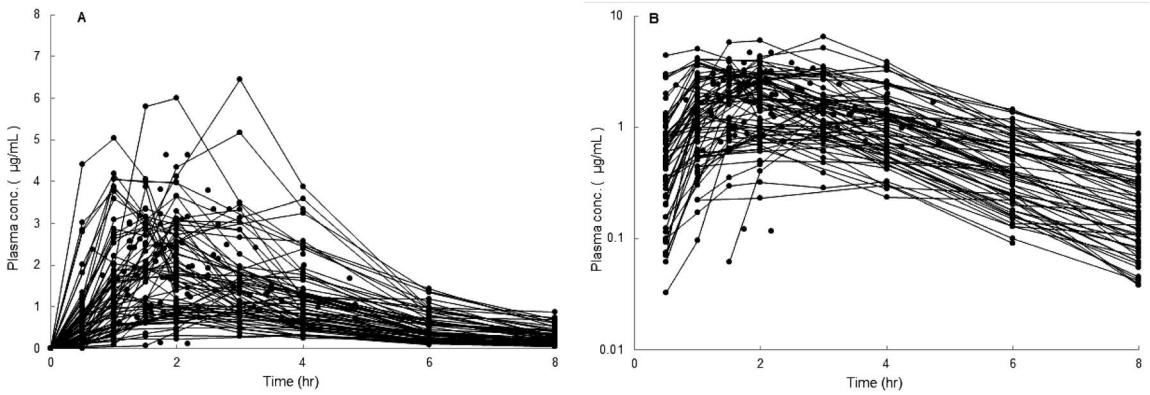


Table 3. Sample size of population used in the analysis

Points/individual	1	2	3	4	5	6	7	8	Total
Number of subjects	73	8	3	4	9	10	9	37	153
Total point	73	16	9	16	45	60	63	296	578

According to goodness-of-fit plots obtained in the basic model, observed plasma concentrations coincided relatively well with individual estimates calculated from population mean parameters (data not shown). When Bayesian estimates for pharmacokinetic parameters (ka, CL/F, Vd/F) and demographic data (Age, WT, Scr, Gender) were plotted, a negative correlation was noted between Bayesian estimate of CL/F and Scr (Fig. 3-A). There was no definite gender difference in the demographic data (Fig. 3-B)。

The development process of the full model is shown in Table 4.

Step 1: Likelihood ratio test were repeated by sequentially including the patients' demographic data as covariates with reference to the results of the basic model. The following model was constructed:

$ka\ (hr^{-1}) = \theta 1$

$CL/F\ (L/hr/kg) = \theta 2 \times Scr + \theta 5$

$Vd/F\ (L/kg) = \theta 3$

$Tlag\ (hr) = \theta 4$

Fig. 3. Relationship between patient demographic data (A: Age, WT and Scr, B: Gender) and un-normalized apparent pharmacokinetic parameters (ka, CL/F and Vd/F) of cefditoren estimated by Bayesian method using the basic model

B: IQR; interquartile range, Dotted line; median, solid line; average, Box＝25 and 75th percentile.

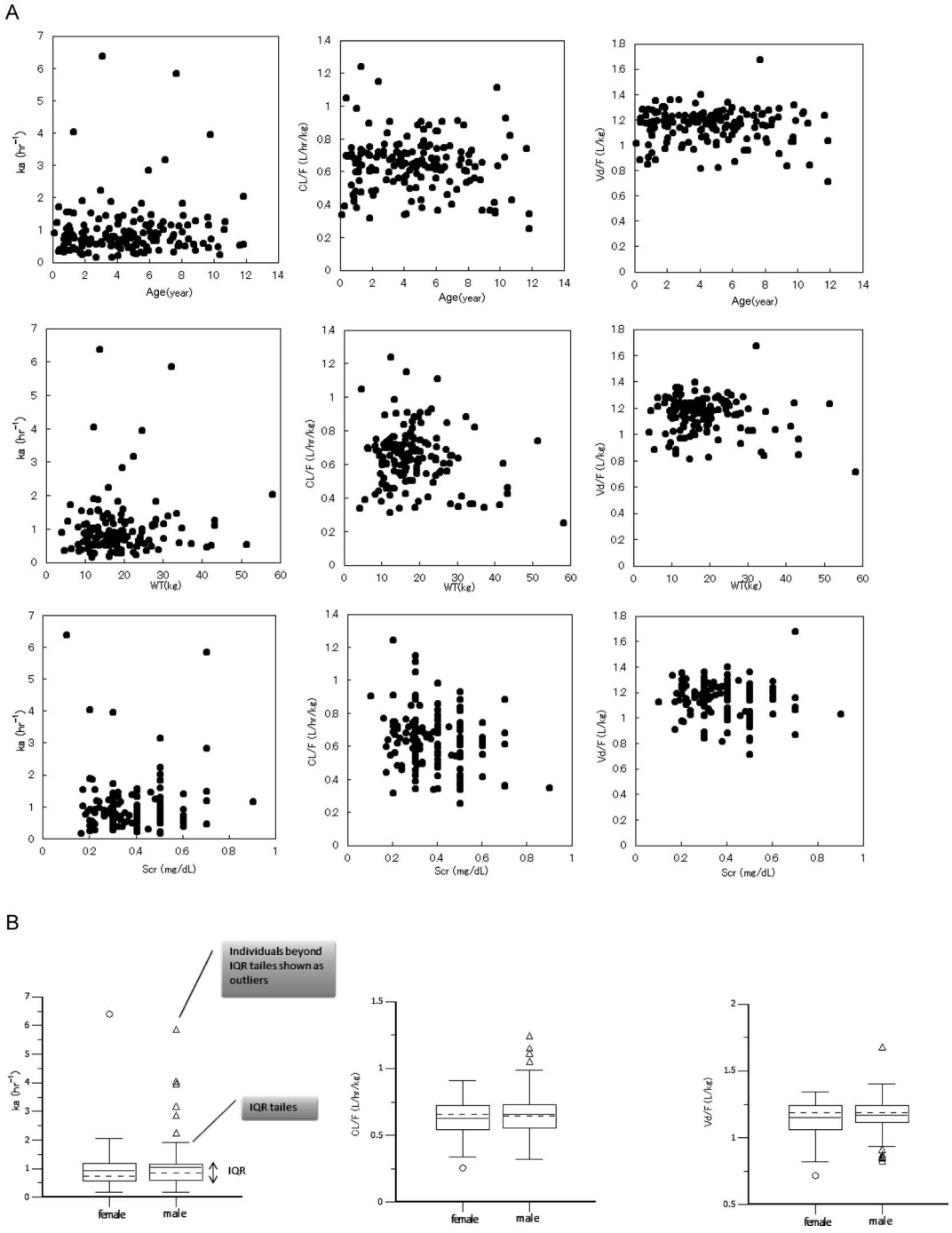


Table 4. Procedure for modifying fixed effect models

Model		Covariate	OBJ	⊿OBJ	Ref model[1)]	df	p value[2)]
Basic Model		ka=θ1 CL/F=θ2 Vd/F=θ3 Tlag=θ4	46.555	—	—	—	—
Additive Model	Step1	CL/F－Scr	37.221	9.334	Basic Model	1	<0.01
	Step2	Tlag－NAT	13.474	23.747	Step1	1	<0.001
Full Model		ka = θ1 CL/F = θ2 × Scr + θ5 Vd/F = θ3 Tlag = θ4 ×（1 + θ6 × NAT[3)]）	13.474	—	—	—	—
Reduced Model		θ2 = 0 FIXED	21.794	8.32		1	<0.01
		θ5 = 0 FIXED	278.135	264.661	Full Model	1	<0.001
		θ6 = 0 FIXED	37.221	23.747		1	<0.001
Final Model		ka = θ1 CL/F = θ2 × Scr + θ5 Vd/F = θ3 Tlag = θ4 ×（1 + θ6 × NAT[3)]）	13.474	—	—	—	—

1): Reference model, 2):χ^2-test (df=1):⊿OBJ >6.63 (p<0.01), ⊿OBJ >10.83 (p<0.001) , 3):NAT:0=Japan, NAT:1= USA

Table 5. Population pharmacokinetic parameters of cefditoren pivoxil in pediatric patients

Population mean parameters		
ka（hr^{-1}）	=	0.527
CL/F (L/hr/kg)	=	−0.474×Scr + 0.82
Vd/F（L/kg）	=	0.77
Tlag (hr)	=	0.282×(1 + 0.435×NAT)
Interindividual variability		
ω(ka)	=	17.23 （%）
ω(CL/F)	=	33.02 （%）
ω(Vd/F)	=	86.66 （%）
ω(Tlag)		—
Intraindividual residual variability		
σ	=	0.428 （μg/mL）

NAT: 0= Japan, NAT:1=USA

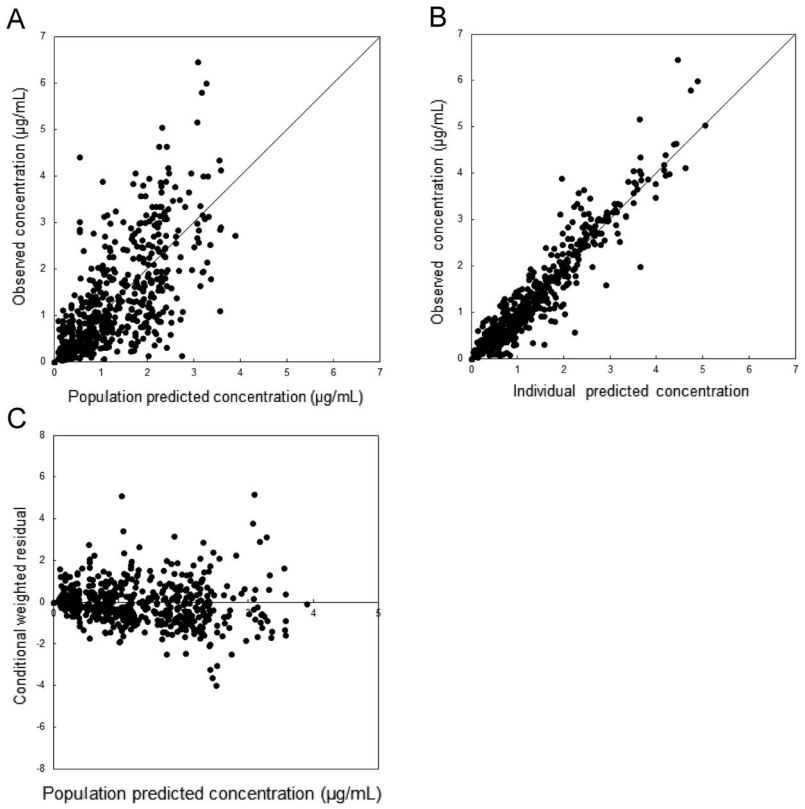
Step 2: When the effect of the country where the clinical trial was conducted (NAT) was examined for each parameter in the above-mentioned model, Tlag was mostly affected ($p<0.001$, degree of freedom (df)＝1, likelihood ratio test). Since there was no gender difference in the patients' demographic data, gender difference was not examined (Fig. 3-B).

Based on the above-mentioned results, a full model was constructed (Table 4).

Finally a reduced model was developed on the basis of the full model, and ΔOBJ was determined against the full model. As a result, THETAs in the full model were all significant, and the full model was identical to the final model (Table 5).

Fig. 4. Goodness-of-fit plots for the final population pharmacokinetic model for cefditoren pivoxil

A: The population predicted concentrations versus the observed concentrations.
B: The individual predicted concentrations versus the observed concentrations.
C: The population predicted concentrations versus the conditional weighted residual.



Model evaluation

Goodness-of-fit plots obtained in the final model are shown in Fig. 4.

Observed plasma concentrations coincided well with the individual estimates calculated from Bayesian estimates, and the individual estimates calculated from the population mean parameters and CWRES were almost equally distributed in the upper and lower sides with the distribution centered around zero. The results of model validation using bootstrap method are shown in Table 6. Ninety-five percentage of calculations (189 out of 200 runs) completed successfully. Mean value or median value of each parameter calculated by the bootstrap method was similar to the parameter estimates from the final model (final estimates). The final estimates for all the parameters were within the range of the 95% confidence intervals obtained from the bootstrap method. Accordingly, the population pharmacokinetic parameters shown in Table 5 were judged to be appropriate.

Table 6. Model validation of population pharmacokinetic parameters of cefditoren pivoxil in pediatric patients (Bootstrap method)

	Final estimates ± S.E. of the model parameters	Mean ± S.E. (Min, Median, Max) Percentile bootstrap 95% CI (lower, upper)	Bootstrap mean (median) / final estimate ratio(%)
	0.527 ± 0.0361	0.893 ± 0.0508	169.4
θ1		(0.365 , 0.581 , 4.14)	(110.2)
		(0.445 , 3.05)	
	-0.474 ± 0.147	-0.484 ± 0.0197	102.1
θ2		(-0.995 , -0.492 , 0.985)	(103.8)
		(-0.914 , -0.0884)	
	0.770 ± 0.0994	1.08 ± 0.0309	140.3
θ3		(0.331 , 0.959 , 2.12)	(124.5)
		(0.541 , 1.96)	
	0.282 ± 0.0251	0.283 ± 0.011	100.4
θ4		(0.00750 , 0.297 , 0.754)	(105.3)
		(0.00750 , 0.712)	
	0.820 ± 0.0676	0.819 ± 0.00909	99.9
θ5		(0.251 , 0.809 , 1.15)	(98.7)
		(0.651 , 1.02)	
	0.435 ± 0.145	1.301 ± 0.118	299.1
θ6		(-0.09 , 0.682 , 4.95)	(156.8)
		(0.0669 , 4.95)	
	0.0297 ± 0.0184	0.383 ± 0.0267	1289.6
ω^2(ka)		(0.00001 , 0.335 , 1.300)	(1127.9)
		(0.00001 , 1.11)	
	0.109 ± 0.0186	0.120 ± 0.00233	110.1
ω^2(CL/F)		(0.00001 , 0.118 , 0.240)	(108.3)
		(0.0736 , 0.178)	
	0.751 ± 0.137	0.360 ± 0.0231	47.9
ω^2(Vd/F)		(0.00001 , 0.258 , 1.05)	(34.4)
		(0.00001 , 0.920)	
	0.183 ± 0.0360	0.231 ± 0.00546	126.2
σ^2		(0.0971 , 0.214 , 0.458)	(116.9)
		(0.127 , 0.381)	

Criterion for success of calculation : " Minimization successful" only

Successful rate of calculation = 95% (189/200)

Calculation of secondary parameters

Bayes estimation was carried out for each subject using the final model to calculate secondary parameters such as C_{max}, T_{max}, AUC, and $t_{1/2}$ (Table 7). The subjects were grouped by dosage. C_{max} was significantly different between the 3 mg/kg group and each of the groups of 6 mg/kg and higher, as well as the 9 mg/kg group and each of the other dose groups (Tukey-Kramer method, $p<0.05$ or $p<0.001$). In addition, AUC showed similar results as in the case of C_{max}. T_{max} was approximately 2 hours at any dose level, and $t_{1/2}$ was approximately 1 hour at any dose level.

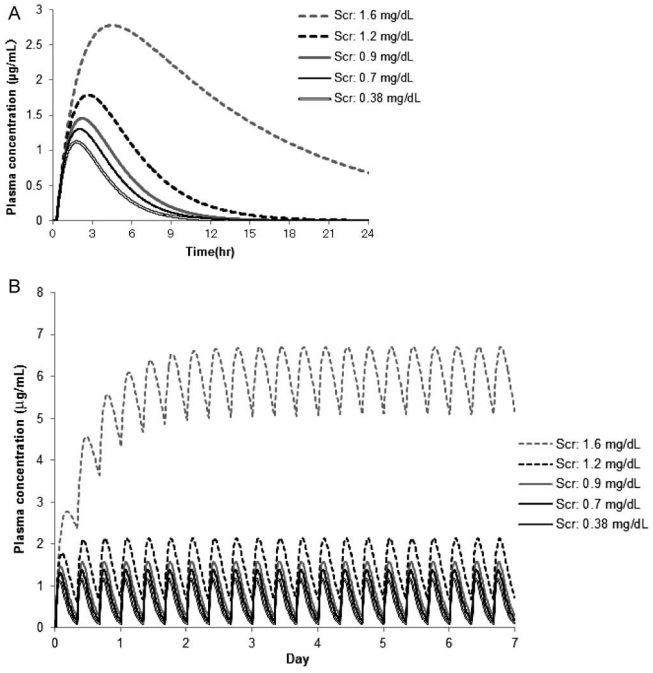
Table 7. Secondary parameters of cefditoren pivoxil calculated by Bayesian method using the final model in pediatric patients

Dose (mg/kg)	n	C_{max} (μg/mL)	T_{max} (h)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)
3.0±0.0	32	1.36±0.58	1.9±0.4	5.71±1.78	1.0±0.5
5.0±0.5	8	2.16±0.71	1.7±0.7	7.92±1.15	1.0±1.2
6.0±0.5	91	2.30±0.78	1.9±0.5	10.01±2.58	1.1±0.6
6.7±0.2	9	2.22±0.78	2.2±0.7	10.78±2.11	1.5±1.4
9.0±0.2	13	3.86±1.05	1.6±0.7	13.53±5.06	0.7±0.5

a: Tukey –Kramer method, p<0.001
b: Tukey –Kramer method, p<0.05

Fig. 5. The simulated plasma concentrations of cefditoren after administration of cefditoren pivoxil (3 mg/kg) for different degrees of renal function

A: single administration, B: repeated administration (3 times daily)
Scr: 0.38 mg/dL : population mean
Scr: 0.7 mg/dL＝2.5 years old, male, HT90 cm[16], GFR: 70 mL/min/1.73 cm^3(Pediatric CKD stage 2、Mild renal failure)
Scr: 0.9 mg/dL＝6 years old, male, HT117 cm[17], GFR: 70 mL/min/1.73 cm^3(Pediatric CKD stage 2、Mild renal failure)
Scr: 1.2 mg/dL＝2.5 years old, male, HT90 cm[16], GFR: 40 mL/min/1.73 cm^3(Pediatric CKD stage 2、Moderate renal failure)
Scr: 1.6 mg/dL＝6 years old, male, HT117 cm[17], GFR: 40 mL/min/1.73 cm^3(Pediatric CKD stage 2、Moderate renal failure)

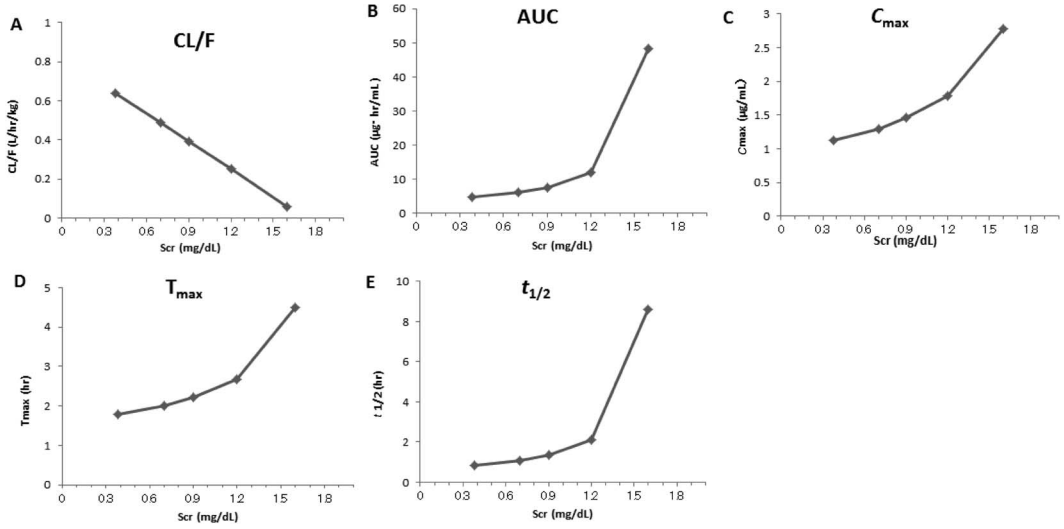


Simulation of pharmacokinetic parameters for different degrees of renal function

The simulated of plasma concentrations under each condition are shown in Fig. 5. CL/F decreased with increasing Scr, (Fig. 6). Under the condition IV, CL/F (0.062 L/hr/kg) decreased to

Fig. 6. Relationship between Scr and pharmacokinetic parameters (CL/F, AUC, C_{max}, T_{max}, $t_{1/2}$) of cefditoren

Dose: 3 mg/kg single administration



1/10 compared to the population mean value (CL/F: 0.64 L/hr/kg). On the other hand, pharmacokinetic parameters and secondary parameters increased with increasing Scr (Fig. 6).

Discussion

CDTR-PI gained manufacturing approval in a tablet form for adults and granule form for children in April 1, 1994 in Japan. Package insert describes the dosing regimen as “In general, cefditoren pivoxil is administered orally to pediatric patients of 3 mg (potency)/kg per dose after meals, *t.i.d.* The dose level shall be adjusted in accordance with age and symptoms.” It has been widely used for various types of pediatric infectious diseases, and its efficacy and safety have been established.

In recent years, however, we have found a lot of drug-resistant strains against existing oral antibiotics in *S. pneumoniae* and *H. influenzae*, the major pathogens for acute otitis media, acute rhinosinusitis, and pneumonia. These diseases become refractory and protracted, which pose a big challenge to antibacterial therapy. CDTR possesses strong antimicrobial activity among existing oral antimicrobials against both of *S. pneumoniae* resistant to penicillin and macrolides, and *H. influenzae* resistant to ampicillin. Accordingly, a high dose of CDTR-PI or amoxicillin (AMPC) is been recommended under the “Guideline for treatment of pediatric acute otitis media, 2009”[19] to treat severe acute otitis media, and moderate acute otitis media that is not improved by AMPC at regular dose, and under the “Guideline for treatment of acute rhinosinusitis, 2010”[20] to treat severe acute rhinosinusitis, and mild or moderate acute rhinosinusitis that is not improved by

AMPC at regular dose. In addition, the "Guideline for treatment of pediatric respiratory tract infections, 2011"[21] also recommends treatment with CDTR-PI at a high dose for pneumonia for which involvement of drug-resistant pathogen is suspected.

Based on the above-mentioned background, clinical trials in pediatric patients with bacterial pneumonia, acute otitis media, or acute rhinosinusitis were performed to determine the efficacy, safety, and plasma CDTR pharmacokinetics of the administration of CDTR-PI at a high dose. As a result, high efficacy and safety were confirmed[10], and the high dosage of CDTR-PI was granted with manufacturing approval in 2012. Accordingly, the current recommended dosing regimen of CDTR-PI is of 6 mg (potency)/kg per dose, *t.i.d.* to treat pediatric patients with bacterial pneumonia, acute otitis media, or acute rhinosinusitis, for which drug-resistant bacterial involvement is highly suspected.

Under these situations, pharmacokinetic information of this compound in pediatric patients is crucially important to determine its efficacy and safety. In this study, a one-compartment model with first-order absorption and lag time was found to be appropriate as the pharmacokinetic model for population analysis of CDTR-PI. Namely, it is necessary to estimate parameters such as ka, CL/F, Vd/F, and Tlag. Moreover, the sampling size such as the total number of sampling points and the number of sampling points per patient is reportedly important for precise estimation of pharmacokinetic parameters of a drug by population analysis[22~25]. Several reports mentioned that a small number of sampling points per patient would lead to a decrease in precision of ka and Tlag, raise the chance of shrinkage of interindividual variability (ETA) or individual weighted residual (IWRES) to 0, and degrade the reliability of empirical Bayes estimates[26,27]. In the present study, we obtained data from abundant number of subjects and blood sampling points for analysis; however, the number of sampling points per patient was not enough because of the patients being children (Table 3). Owing to this big sample size as a whole, it was possible to estimate 4 population pharmacokinetic parameters. However, despite improvement in the model precise estimation of ETA for Tlag was not possible because of the small number of sampling points per patient. Thus, we used a model without interindividual variability, for the population pharmacokinetic analysis.

Through above-mentioned improvements, population pharmacokinetic analysis on CDTR-PI was carried out in pediatric patients, and a model where CL/F was affected by Scr was obtained, and CL/F was found to decrease along with increasing Scr. Such results were considered appropriate, since CDTR is a drug excreted renally[28]. In addition, Tlag was affected by the difference in countries where the clinical trials were conducted. Fine granules were used in Japan, and suspensions in the USA; which is thought to contribute to the current results. Lag time was longer in the USA (suspensions) than in Japan (fine granules), but the difference was minimal, such as 0.12 hour.

Bayes estimation was carried out for each subject using the final model to calculate second-

ary parameters such as C_{max}, T_{max}, AUC, and $t_{1/2}$ (Table 7). AUC and C_{max} increased significantly with increase in dose. Thus, in the oral administration of CDTR-PI to pediatric patients, plasma CDTR concentrations is expected to increase significantly along with increased doses, suggesting high efficacy.

Based on the fact that CL/F is affected by Scr, pharmacokinetic parameters were calculated in the oral administration of CDTR-PI at 3 mg/kg to pediatric patients with impaired renal function, and plasma concentrations of CDTR were simulated. CL/F was shown to decrease proportionally with increasing Scr, and CL/F decreased to 1/10 compared to the population mean in condition IV (Fig. 6-A). Accordingly under the condition IV, the blood concentration was relatively high after repeated administration 3 times daily, and C_{max} was 6～7 μg/mL at the steady state (Fig. 5). This C_{max} was, however, within the blood concentration level for which tolerability was confirmed in the clinical trial conducted in the USA (3～9 mg/kg). In addition, secondary parameters such as AUC, C_{max}, T_{max}, and $t_{1/2}$ all increased with increasing Scr. Particularly AUC and $t_{1/2}$ increased with increasing Scr significantly (Fig. 6-B, E).

The relationship between renal functions and pharmacokinetics of this drug has been reported in clinical trials in adults, which confirmed the elevation of plasma concentrations and prolongation of half-life along with impairment in renal functions[29,30]. Accordingly, it has been stated that greatest care should be taken to the administration of this drug to adult patients with impaired renal function. In the present study, the elevation of plasma concentrations and prolongation of the half-life were also suggested in pediatric patients with impaired renal function as in the case of adult cases. Even in condition IV having the longest half-life, the blood concentration reached steady state 2 days after the start of repeated administration (3 times daily).

Finally, pediatric population pharmacokinetic parameters allow us to simulate pharmacokinetics for various patient demographic data administered with various dosing regimens, which will lead to determination of efficacy or safety of this drug.

Conclusion

Population pharmacokinetic parameters were obtained using plasma CDTR concentrations for oral administration of CDTR-PI after meals to pediatric patients. This analysis has revealed that Scr affects the CL/F of CDTR and the location where the clinical trial was conducted (NAT) affects Tlag.

Therefore oral administration of CDTR-PI to a pediatric patient with impaired renal function was suggested to show a delay in T_{max}, increases in AUC and C_{max}, and prolongation of $t_{1/2}$ with increasing Scr.

As mentioned above, population mean parameters of CDTR, interindividual variability, and intraindividual residual variability when CDTR-PI was orally administered to pediatric patients

were obtained, which is sure contribute to simulation of its plasma concentrations in patients with various backgrounds and to speculation of its efficacy and safety.

Conflict of interest

The authors declare no conflict of interest.

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