# Population pharmacokinetics of cefditoren pivoxil in non-infected adults

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Population pharmacokinetic analysis was conducted on cefditoren pivoxil (CDTR-PI), a third generation oral antibiotic to evaluate the effect of covariates on pharmacokinetic parameters. Plasma concentrations of cefditoren (CDTR, total number of sampling points: 2864) obtained from healthy adult subjects, elderlies, and subjects with renal dysfunction (287 subjects) after CDTR-PI administration as well as demographic data of those subjects were used for analysis. We conducted the population pharmacokinetic analysis of CDTR-PI using a nonlinear mixed effects modeling (NONMEM) method. A one-compartment model with a first-order absorption and lag time fitted well to plasma concentration-time curve for CDTR.

The subject covariate significantly affecting pharmacokinetic parameters of CDTR-PI was demonstrated by population pharmacokinetic analysis. The absorption rate constant (ka: $hr^{-1}$) of CDTR-PI decreased with age, total clearance adjusted by bioavailability (CL/F: L/hr/kg) increased with increasing creatinine clearance adjusted by body weight (Ccr: mL/min/kg) and volume of distribution adjusted by bioavailability (Vd/F: L/kg) decreased with increasing body weight (WT: kg). In addition, the lag time (Tlag: hr) depends on formulation (tablet or granule) of CDTR-PI and the absorption lag time of the tablet was longer than that of the granule.

We could obtain the population mean parameters of CDTR-PI together with interindividual variability and intraindividual residual variability after oral administration of CDTR-PI to adult subjects. In the future, this information will enable us to simulate the plasma concentrations of CDTR in subjects with various demographic backgrounds, which contributes to future examination of the efficacy and safety of CDTR-PI.

## 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 for which gastrointestinal absorption has been enhanced by making pivaloyloxymethyl ester at the C4-carboxylic acid of cefditoren (CDTR) that has a broad spectrum and strong antibacterial activity[2] against aerobic and anaerobic Gram-positive bacteria as well as Gram-negative bacteria[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, 4～6]. This compound was approved in Japan in 2005, and the dosing regimen for an adult is three times daily at 200 mg as maximum. As of March 2012, this compound was approved and marketed in 29 countries including not only Asian nations such as Korea and China, but also European countries and the United States of America. One time dosage of 200 mg has been commonly used for adult patients.

Pharmacokinetics of this compound have been investigated in clinical trials in adult subjects and reported[7～11], however, population pharmacokinetic analysis in adult has not been conducted yet.

In this analysis, population pharmacokinetics were investigated on CDTR-PI, using plasma concentrations obtained in several clinical pharmacological studies in Japan and the USA as well as demographic data of the subjects. As a result, the covariates that are related to pharmacokinetic parameters of CDTR-PI were clarified to determine the pharmacokinetics of CDTR after CDTR-PI administration. In addition, it would be also possible to simulate plasma concentrations of CDTR on the basis of hypothesized particular demographic data, which would contribute to evaluation of the efficacy and safety of this compound.

## Materials and Methods

### Pharmacokinetic sampling

Plasma CDTR concentrations (total sampling points: 2864) obtained from 287 subjects in 5 clinical trials (clinical pharmacology studies) that were conducted in Japan between 1987 and 1997 and 6 clinical trials (clinical pharmacology studies)[5, 8～10, 12] in the USA between 1998 and 1999, and demographic data of those subjects were used for analysis (Table 1). These studies were all performed in accordance with the declaration of Helsinki, the ethics committee approval, and the informed consent of all subjects. CDTR-PI was administered at doses of 1.3 mg/kg～5.9 mg/kg (100～300 mg/man: Japan) or 2.1 mg/kg～8.5 mg/kg (400 mg/man: USA). The plasma CDTR concentrations were measured with Bioassay method where *Escherichia coli* NIHJ JC-2 was used as a test bacterial strain (quantitation limit, 0.025 $\mu$g/mL)[13], or HPLC-UV method

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

| Trial type | Location | Year | Formulation | Dose (mg/man) | Sample collection* (hr) | Assay | LLOQ (μg/mL) |
|---|---|---|---|---|---|---|---|
| Phase I Study | Japan | 1987-1988 | Tablet | 100-200 | 0.5, 1, 2, 3, 6, 8, 12, 24 | Bioassay | 0.025 |
| Bioequivalence Study | | 1995-1997 | | | 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8 | | |
| | | 1995-1996 | Granule | | | | |
| Clinical Pharmacology Study | | 1991 | Tablet | | 1, 2, 4, 6, 8, 12, 24 | | |
| Bioequivalence Study | USA | 1998 | Tablet | 200-400 | 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 24 | HPLC | 0.05 |
| Clinical Pharmacology Study | | 1998-1999 | | | 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, (16), 24 | | |
| | | | | | | LC-MS/MS | 0.02 |

*; after administration

(quantitation limit, 0.05 $\mu$g/mL)[7, 14], or LC-MS/MS method (quantitation limit, 0.02 $\mu$g/mL). The plasma concentrations of CDTR and demographic data of the subjects used for analysis were collected retrospectively from medical records and clinical study reports.

**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 parameter, interindividual variability, and intraindividual residual variability), and to estimate the pharmacokinetic parameters of each subject by Bayesian method.

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 there is a difference in weight between Americans and Japanese (Table 2), the dose was adjusted by body weight (mg/kg) and thus the parameters of CL/F and Vd/F were also adjusted by body weight.

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

C(t): plasma CDTR concentration ($\mu$g/mL) at time after CDTR-PI administration
Dose: single dosage (mg/kg)
ka: absorption rate constant ($hr^{-1}$)
F: bioavailability
Vd/F: volume of distribution adjusted with F (L/kg)
kel (=(CL/F) / (Vd/F)): elimination rate constant ($hr^{-1}$)
CL/F: total clearance adjusted with 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: $Cp_{ij}=\overline{C}p_{ij}+\varepsilon_{ij}$

$P_i$: individual pharmacokinetic parameter
$\overline{P}$: population mean of pharmacokinetic parameter
$Cp_{ij}$: individual plasma concentration
$\overline{C}p_{ij}$: estimated plasma concentration
$\eta_i$: error of interindividual variability in pharmacokinetic parameter (the normally distributed interindividual random effect of mean 0 and variance $\omega^2$)
$\varepsilon_{ij}$: error of intraindividual residual variability in plasma concentrations (the normally distributed intraindividual random effect of mean 0 and variance $\sigma^2$)

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

The following steps were taken to establish a full model.

Step 1: Demographic data (age, weight: WT, creatinine clearance: Ccr) were sequentially related to the pharmacokinetic parameters (ka, CL/F, Vd/F, Tlag) in the basic model to build additive models. A likelihood ratio test was conducted to assess the significance of decrease of OBJ (Δ objective 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.

Demographic data were further sequentially related to the selected model in the above to build a new additive model, and a likelihood ratio test was conducted on the significance of ΔOBJ in this model to that in the above-mentioned model.

This procedure was repeated until no more additive model with significant ΔOBJ could be built even though demographic data were sequentially related to any of pharmacokinetic parameters. The additive model that was finally selected was designated as a final model in Step 1.

Step 2: Bayesian estimates of individual pharmacokinetic parameters obtained in population pharmacokinetic analysis using the basic model and the demographic data were plotted. With reference to this result, if the relationship between them is well described by introducing a switch point into demographic values, such a compartment was adopted in constructing a model. A likelihood ratio test was carried out for the models with and without such a compartment (Final model at Step 1).

Step 3: Using the model selected in Steps 1 and 2 by incorporating the demographic data, the effects of factors such as the location where the clinical trial was conducted (Japan or the USA) , formulation of drug product (tablet or granule), and the effect of the gender were 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 criteria for judging the significance of ΔOBJ was set to be a significance level of 0.001 or lower in accordance with $X^2$ distribution.

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 Bayesian 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 ware reconstructed by resampling the subjects 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.

## Results

### Demographic data

The demographic data of the subjects 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), creatinine clearance adjusted by body weight (Ccr; mL/min/kg) converted from creatinine clearance (Ccr; mL/min) that was calculated with the Cockcroft-Gault method[15] from serum creatinine concentration (Scr; mg/dL), the country where a clinical trial was conducted (Japan or the USA), and formulation (FM; tablet or granule) of drug product. 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 287, among which 111 subjects were from studies conducted in Japan (72 subjects administered with tablets, and 39 subjects administered with granules) and 176 subjects from the study conducted in the USA (all administered with tablets). When categorized by gender, there were 209 males and 78 females. The average dose was 3.75±1.85 mg/kg (mean ±S.D.), and the minimum, median and maximum values of doses were 1.30, 3.60, and 8.47 mg/kg, respectively. When the demographic data of the subjects were plotted, age was related with Ccr and Ccr tended to decrease with age. There was no definite relationships between gender and patients' demographic data (Fig. 1).

### Plasma CDTR concentrations

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.

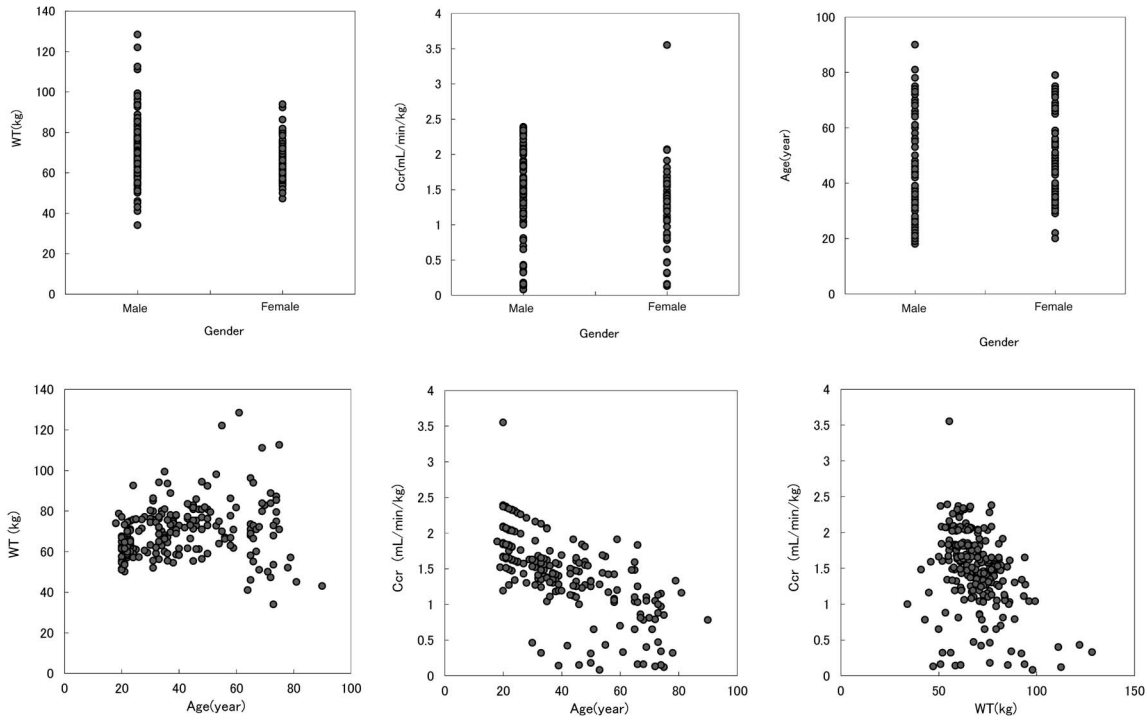
Concerning a structure model, a model with or without lag time and a transit compartment model for one-compartment model and two-compartment model were evaluated (data not

**Table 2. Demographic data of the subjects**

| | | Mean ± S.D. | Minimum | Median | Maximum |
|---|---|---|---|---|---|
| Japan ( n=111 ) | Dose (mg/kg) | 2.11 ± 1.06 | 1.30 | 1.67 | 5.88 |
| ( FM: tablet=72, granule=39 ) | Age (year) | 27.83 ± 15.78 | 20.00 | 22.00 | 90.00 |
| ( Gender : male=107, female=4 ) | WT (kg) | 61.00 ±7.40 | 34.00 | 61.00 | 77.00 |
| | Ccr (mL/min/kg) | 1.87 ± 0.41 | 0.16 | 2.03 | 2.39 |
| USA (N=176) | Dose (mg/kg) | 4.79 ± 1.44 | 2.13 | 5.13 | 8.47 |
| ( FM: tablet=176 ) | Age (year) | 43.60 ± 14.90 | 18.00 | 39.00 | 75.00 |
| ( Gender : male=102, female=74 ) | WT (kg) | 74.20 ± 12.70 | 47.20 | 73.50 | 128.40 |
| | Ccr (mL/min/kg) | 1.30 ± 0.54 | 0.08 | 1.40 | 3.55 |
| Total (N=287) | Dose(mg/kg) | 3.75 ± 1.85 | 1.30 | 3.60 | 8.47 |
| ( FM: tablet=248, granule=39 ) | Age(year) | 37.52 ± 17.05 | 18.00 | 33.00 | 90.00 |
| ( Gender : male=209, female=78 ) | WT (kg) | 69.07 ± 12.67 | 34.00 | 66.90 | 128.40 |
| | Ccr (mL/min/kg) | 1.52 ± 0.57 | 0.08 | 1.59 | 3.55 |

FM: formulation

**Fig. 1. Relationships in patient demographic data**



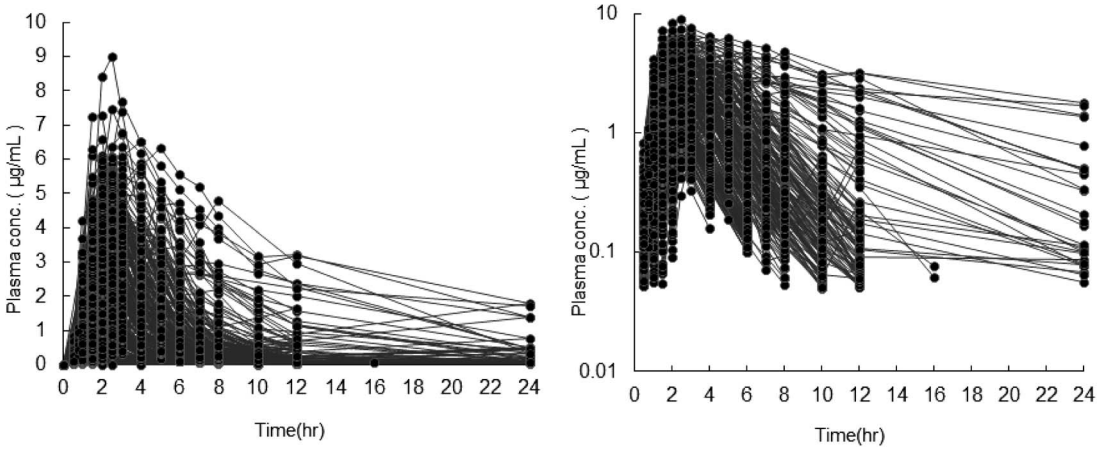

shown). Considering the presence or absence of the convergence of calculations in NONMEM and the OBJ value, a one-compartment model with first-order absorption and lag time was considered the most suitable structure model for population pharmacokinetic analysis of CTDR-PI.

**Population pharmacokinetic analysis**

Population mean parameters obtained in the basic model were as follows: ka ($hr^{-1}$)＝1.04, CL/F (L/hr/kg)＝0.337, Vd/F (L/kg)＝0.67, Tlag (hr)＝0.89, interindividual variability: $\omega$ (ka)＝

**Fig. 2. Plasma concentration-time profiles of cefditoren determined in all the clinical trials**

The plasma concentrations of cefditoren obtained from healthy adult subjects, elderlies, and subjects with renal dysfunction (287 subjects) after oral administration of cefditoren pivoxil (1.30～8.47 mg/kg).




84.0%, $\omega$ (CL/F)＝46.6%, $\omega$ (Vd/F)＝29.4%, intraindividual residual variability: $\sigma$＝0.465 $\mu$g/mL. Interindividual variability of Tlag was not estimated.

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, and such individual estimates and CWRES were almost equally distributed in the upper and lower sides with the distribution centered around zero (data not shown). When Bayesian estimates for pharmacokinetic parameters (ka, CL/F, Vd/F) and demographic data (age, WT, Ccr, gender) were plotted, the following tendencies were noted: a negative correlation between Bayesian estimate of ka and age, a negative correlation between Bayesian estimate of CL/F and age, and a positive correlation between Bayesian estimate of CL/F and Ccr. In addition, a negative correlation was found between Bayesian estimate of Vd/F and WT (Fig. 3-A). On the other hand, there was no definite gender difference in the demographic data (Fig. 3-B).

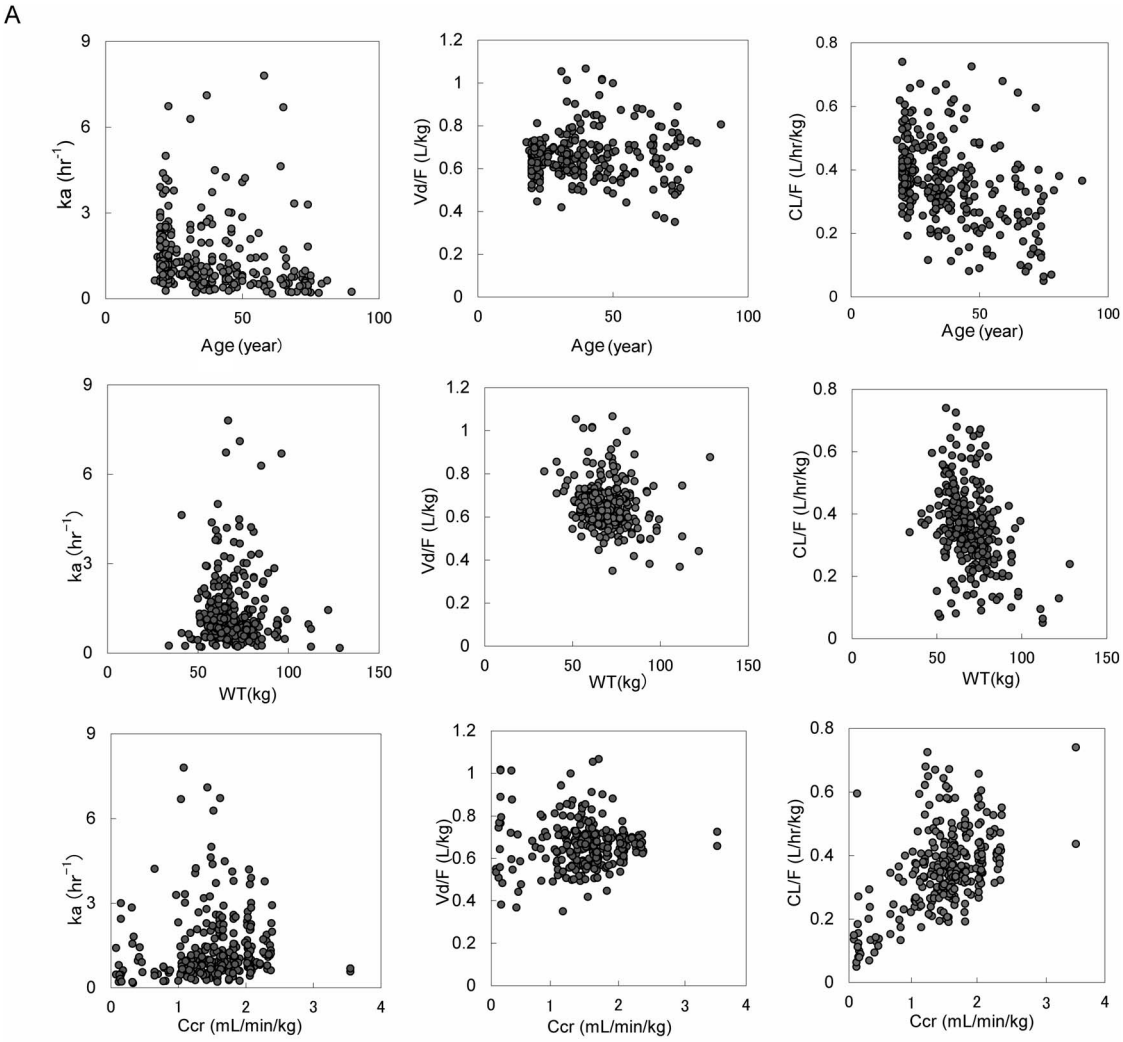
The development process of the full model is shown in Table 3.

As Step 1, likelihood ratio test where each subjects' demographic data is sequentially included as a covariate into pharmacokinetic parameter, with reference to the results of plotting in the basic model, was repeated to construct an additive model. Based on the plots of the Bayesian estimates of pharmacokinetic parameters versus the demographic data (Fig. 3) as well as general knowledge on the relationship between Ccr and CL/F, CL/F was considered to have leveled off along with an increase in Ccr.

Therefore, as Step 2, a switch point for Ccr (0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5 mL/min/kg) was introduced into the model selected in Step 1 for investigation. As a result, $\Delta$OBJ was found to be the largest and most significant ($p < 0.01$, drgree of freedom(df)＝2, likelihood ratio test)

**Fig. 3. Relationship between demographic data (A: Age, WT and Ccr, B: Gender) and unnormalized 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.



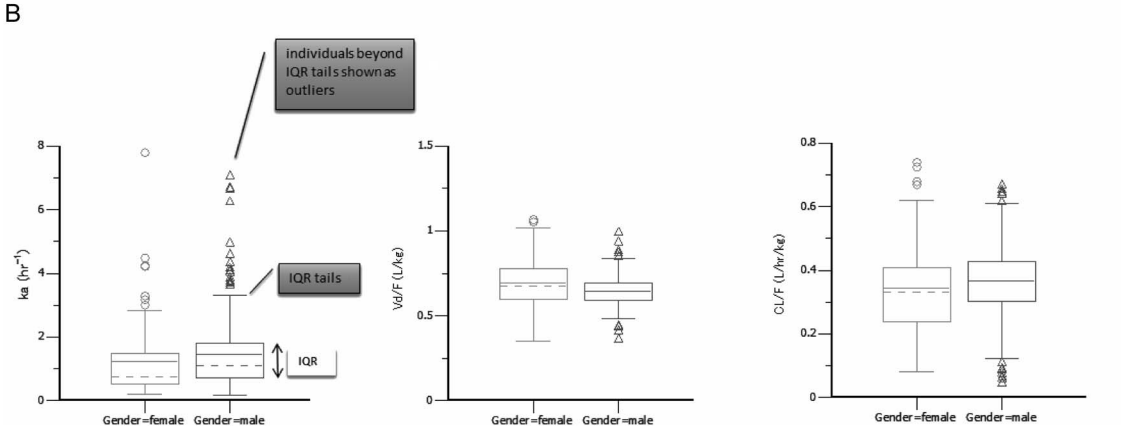



**Table 3. Covariate model building**

| Model | Step | Model No. | Covariate | OBJ | ⊿OBJ | Ref model[1] | df | p value[2] | |
|---|---|---|---|---|---|---|---|---|---|
| Basic Model | | | ka = θ1<br>CL/F = θ2<br>Vd/F = θ3<br>Tlag = θ4 | 62.62 | - | - | - | - | |
| Additive Model | Step 1 | 1 | CL/F－Ccr | -109.95 | 172.566 | Basic Model | 1 | <0.001 | |
| | | 2 | ka－Age | -141.587 | 31.639 | 1 | 1 | <0.001 | |
| | | 3 | Vd/F－WT | -156.493 | 14.906 | 2 | 1 | <0.001 | |
| | | 4 | Tlag－Age | -161.849 | 5.356 | 3 | 1 | <0.05 | |
| | Step 2 | 5 | Discrimination value of Ccr:1.25 | -172.760 | 10.911 | 4 | 2 | <0.01 | |
| | Step 3 | 6 | Tlag－FM[3] | -217.806 | 45.046 | 5 | 1 | <0.001 | Full Model |
| Full Model | | 6 | ka = θ1×Age + θ6<br>CL/F = θ2 × Ccr + θ5 (Ccr ≤ 1.25 mL/min/kg)<br>CL/F = θ9 × Ccr + θ10 (Ccr > 1.25 mL/min/kg)<br>Vd/F = θ3 × WT + θ7<br>Tlag = （θ4 × Age + θ8） ×（1 + θ11 × FM[3]） | -217.806 | - | - | - | - | |
| Reduced Model | | 7 | θ4 = 0 FIXED | -215.521 | 2.285 | | 1 | NS | Final Model |
| Final Model | | 7 | ka = θ1×Age + θ6<br>CL/F = θ2 × Ccr + θ5 (Ccr ≤ 1.25 mL/min/kg)<br>CL/F = θ9 × Ccr + θ10 (Ccr > 1.25 mL/min/kg)<br>Vd/F = θ3 × WT + θ7<br>Tlag = θ8 ×（1 + θ11 × FM[3]） | -215.521 | - | - | - | - | |

1) Reference model
2) $\chi^2$-test (df=1): ΔOBJ＞3.84 (p＜0.05), $\chi^2$-test (df=2): ΔOBJ＞5.99 (p＜0.05), NS: Not significant, Forward criteria: p＜0.05, Backward criteria: p＜0.001
3) FM: 0=tablet, FM: 1=granule

**Table 4. Population pharmacokinetic parameters of cefditoren pivoxil**

| | | |
|---|---|---|
| Population mean parameters | | |
| ka（$hr^{-1}$） | = | -0.0155 × Age + 1.69 |
| CL/F (L/hr/kg) | = | 0.230 × Ccr + 0.0798 （Ccr ≤ 1.25 mL/min/kg） |
| | | 0.109 × Ccr + 0.190 （Ccr >1.25 mL/min/kg） |
| Vd/F （L/kg） | = | -0.00502 × WT + 1.04 |
| Tlag (hr) | = | 0.894 ×（1-0.298 × FM） |
| Interindividual variability | | |
| ω（ka） | = | 80.3% |
| ω（CL/F） | = | 32.1% |
| ω（Vd/F） | = | 28.4% |
| ω（Tlag） | | — |
| Intraindividual residual variability | | |
| σ | = | 0.457 （μg/mL） |

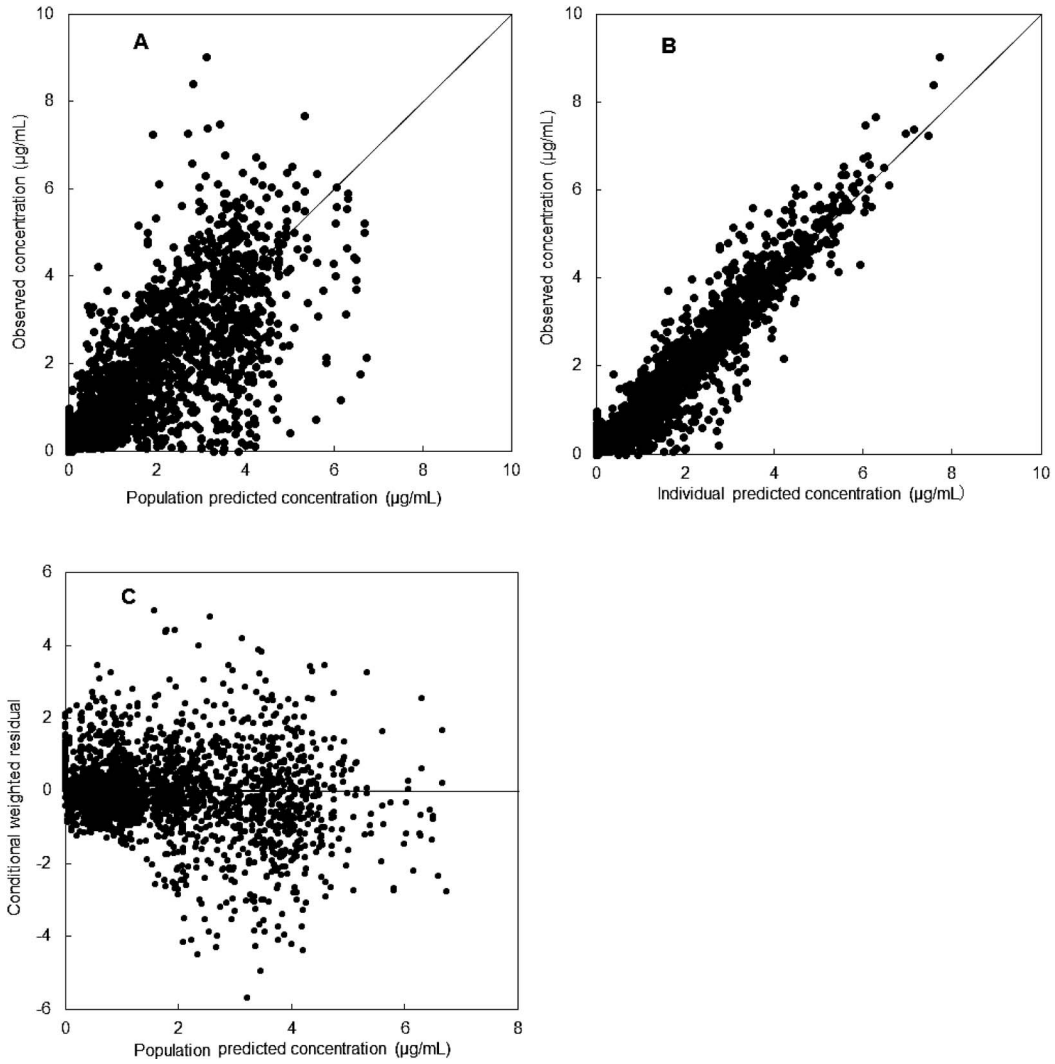
FM: 0=tablet, FM: 1=granule

when a switch point for Ccr at 1.25 mL/min/kg was included in CL/F .

As Step 3, when the effect of product form (FM: formulation) on each pharmacokinetic parameter was examined in the above-mentioned model. Tlag was the one mostly influenced (p＜0.001, df＝1, likelihood ratio test). Additionally, the effect of the clinical trial location on each

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

A: Population predicted concentrations versus observed concentrations.
B: Individual predicted concentrations versus observed concentrations.
C: Population predicted concentrations versus conditional weighted residual.




pharmacokinetic parameter was examined, which resulted in no significant effect on any of the pharmacokinetic parameters (full model).

Since there was no gender difference in the subjects' demographic data, gender difference was not examined (Fig. 3-B).

Finally a reduced model was developed on the basis of the full model, and ΔOBJ was determined against the full model. As a result, a coefficient of age (θ4) was not significant against Tlag, which was then excluded to produce the final model (Table 3).

**Table 5. Results of the bootstrap analysis**

| | 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(%) |
|---|---|---|---|
| θ1 | -0.0155 ± 0.00234 | -0.0150 ± 0.000224<br>( -0.0229 , -0.0148 , -0.00330 )<br>( -0.0200 , -0.00873 ) | 96.8<br>(95.5) |
| θ2 | 0.230 ± 0.0270 | 0.234 ± 0.00207<br>( 0.148 , 0.233 , 0.311 )<br>( 0.185 , 0.289 ) | 101.7<br>(101.3) |
| θ3 | -0.00502 ± 0.00115 | -0.00497 ± 0.0000940<br>( -0.00798 , -0.0051 , -0.0000200 )<br>( -0.00738 , -0.00233 ) | 99.0<br>(100.6) |
| θ5 | 0.0798 ± 0.0195 | 0.0786 ± 0.00152<br>( 0.0265 , 0.0770 , 0.134 )<br>( 0.0446 , 0.1205 ) | 98.5<br>(96.5) |
| θ6 | 1.69 ± 0.135 | 1.67 ± 0.0154<br>( 0.617 , 1.69 , 2.21 )<br>( 1.38 , 2.01 ) | 98.8<br>(100.0) |
| θ7 | 1.04 ± 0.0882 | 1.03 ± 0.00929<br>( 0.307 , 1.04 , 1.31 )<br>( 0.81700 , 1.23 ) | 99.0<br>(100.0) |
| θ8 | 0.894 ± 0.00718 | 0.894 ± 0.000558<br>( 0.875 , 0.894 , 0.912 )<br>( 0.880 , 0.908 ) | 100.0<br>(100.0) |
| θ9 | 0.109 ± 0.0209 | 0.108 ± 0.00222<br>( 0.0208 , 0.108 , 0.173 )<br>( 0.0603 , 0.164 ) | 99.1<br>(99.1) |
| θ10 | 0.190 ± 0.0369 | 0.194 ± 0.00386<br>( 0.0754 , 0.195 , 0.341 )<br>( 0.0912 , 0.278 ) | 102.1<br>(102.6) |
| θ11 | -0.298 ± 0.0181 | -0.304 ± 0.0038<br>( -0.491 , -0.302 , -0.089 )<br>( -0.469 , -0.248 ) | 102.0<br>(101.3) |
| $\omega^2$(ka) | 0.645 ± 0.0801 | 0.632 ± 0.00842<br>( 0.0673 , 0.641 , 0.832 )<br>( 0.442 , 0.808 ) | 98.0<br>(99.4) |
| $\omega^2$(CL/F) | 0.103 ± 0.0156 | 0.100 ± 0.00115<br>( 0.0714 , 0.0988 , 0.135 )<br>( 0.0754 , 0.130 ) | 97.1<br>(95.9) |
| $\omega^2$(Vd/F) | 0.0809 ± 0.0160 | 0.0912 ± 0.00606<br>( 0.0405 , 0.0795 , 0.799 )<br>( 0.0507 , 0.150 ) | 112.7<br>(98.3) |
| $\sigma^2$ | 0.209 ± 0.0175 | 0.207 ± 0.00136<br>( 0.161 , 0.206 , 0.249 )<br>( 0.177 , 0.244 ) | 99.0<br>(98.6) |

Criterion for success of calculation: “Minimization successful” only
Successful rate of calculation=86% (172/200)

Population pharmacokinetic parameters obtained in the final model are shown in Table 4.

## Model evaluation

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

Observed plasma concentrations were coincided well with the individual estimates calculated from Bayesian estimates, t 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 5. Eighty-six percentage of calculations (172 runs 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 empirical 95% confidence intervals obtained from the bootstrap method. Accordingly, the population pharmacokinetic parameters shown in Table 4 were judged to be appropriate.

## Discussion

Population pharmacokinetic parameters of CDTR-PI were determined using plasma CDTR concentrations (2864 points) when CDTR-PI was orally administered to 287 subjects at 1.3～8.5 mg/kg after meals. The location where a clinical trial was conducted did not affect any of the pharmacokinetic parameters.

This model showed lowered ka (absorption rate) of CDTR-PI with age. In general, the intestinal plasma flow volume and gastrointestinal motility are decreased in the elderly[16~21], which may result in lowered absorption rate. The physicochemical properties of CDTR-PI itself, however, can be a causative factor as well. The solubility of CDTR-PI in water has been reported to be as low as *ca.* 80 $\mu$g/mL[22]. In addition, the solubility of CDTR-PI is relatively high in the acidic region (pH1～2), while it is lowered to 1/10～1/100 at pH3 or higher[23]. Since gastric pH in the elderly is generally higher than that in young adults[16], the solubility of CDTR-PI in the stomach may get lowered with age. The relationship between gastric pH and absorbance was examined in an *in vivo* study using dogs, which showed decreases in both the absorbed amount and absorption rate along with an increase in pH[24]. Moreover, a clinical trial revealed that concomitant use of CDTR-PI with antacid tablets lowered the absorbed amount and absorption rate of this compound[12]. It is also known that the volume of gastric mucosal fluid decreases with age[16], and thus the solubility of CDTR-PI may become lowered with age due to the factors of pH and water contents. It would contribute to lowered absorption rate of CDTR-PI. Finally, the population pharmacokinetic analysis results were considered not to be contradictory to the discussion mentioned in the above.

Next, Ccr affected CL/F of CDTR, and CL/F was reduced along with decreased Ccr (deterioration of the renal function) in this model. These results seem to be reasonable, since CDTR-PI is mainly excreted via the kidney[25]. When the renal function was within the normal range (Ccr＞1.25 mL/min/kg), the effect of Ccr was rather mild. The renal function is known to deteriorate

with age in general, and the average GFR in the subjects whose renal function is normal at respective age is expressed in the following equation[26].

$$\text{GFR (mL/min/1.73 cm}^3\text{)} = -1.163 \times (\text{Age}) + 157.0$$

Using this equation, GFR for each age was calculated in the range from 25 to 85 years old, and the population mean pharmacokinetic parameters in case of body weight at 70 kg are shown in Table 6. GFR was assumed to be approximated by Ccr. Plasma concentrations of CDTR after single or repeated oral administration of CDTR-PI at 1.5 mg/kg (*ca.* 100 mg/man) to adult subjects were simulated at each age using the population mean parameters (Fig. 5-A, E). As a result, ka decreased with age in the absorption process, and CL/F decreased along with age-dependent degrease in GFR in the elimination process. Vd/F was, however, constant regardless of age, and thus $T_{1/2}$ was prolonged. In other words, $C_{max}$ of CDTR was decreased and AUC tended to increase with age after oral administration of CDTR-PI to adult subjects with normal renal function. On the other hand, when CDTR-PI was administered repeatedly three times a day, the plasma CDTR concentration level reached a steady state immediately after administration, and there was no accumulation at any age.

According to the population mean parameters of CDTR-PI obtained in this study, Ccr at the age of 65 was decreased by 36% compared to that at the age of 25; however there was only 11% decrease in the comparison of CL/F (Table 6). This indicates that glomerular filtra-

**Table 6. Estimates of pharmacokinetic parameters**

| Age (year) | WT (kg) | Dose (mg/kg) | Ccr[1] (mL/min) | Ccr (mL/min/kg) | ka ($hr^{-1}$) | CL/F (L/hr/kg) | Vd/F (L/kg) | kel ($hr^{-1}$) | Tlag (hr) | Cmax,single[2] (μg/mL) | Cmax,ss[3] (μg/mL) | AUC[4] (μg·hr/mL) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 25 | 70 | 1.5 | 127.9 | 1.83 | 1.303 | 0.389 | 0.689 | 0.565 | 0.894 | 1.15 | 1.16 | 3.85 |
| 45 | 70 | 1.5 | 104.7 | 1.50 | 0.993 | 0.353 | 0.689 | 0.513 | 0.894 | 1.07 | 1.11 | 4.24 |
| 65 | 70 | 1.5 | 81.4 | 1.16 | 0.683 | 0.347 | 0.689 | 0.504 | 0.894 | 0.93 | 0.98 | 4.32 |
| 85 | 70 | 1.5 | 58.1 | 0.83 | 0.373 | 0.271 | 0.689 | 0.393 | 0.894 | 0.78 | 0.95 | 5.54 |

1) Ccr was assumed to be approximated by GFR
2) Cmax at single administration
3) Cmax at steady state
4) $AUC_{0-\infty}$ at single administration=$AUC_\tau$ (AUC of the dosing interval at steady state) at repeated administration

**Fig. 5. Simulated plasma concentrations of cefditoren after oral administration of cefditoren pivoxil at 1.5 mg/kg (*ca.* 100 mg/man) to adult subjects at each age using the population mean parameters**

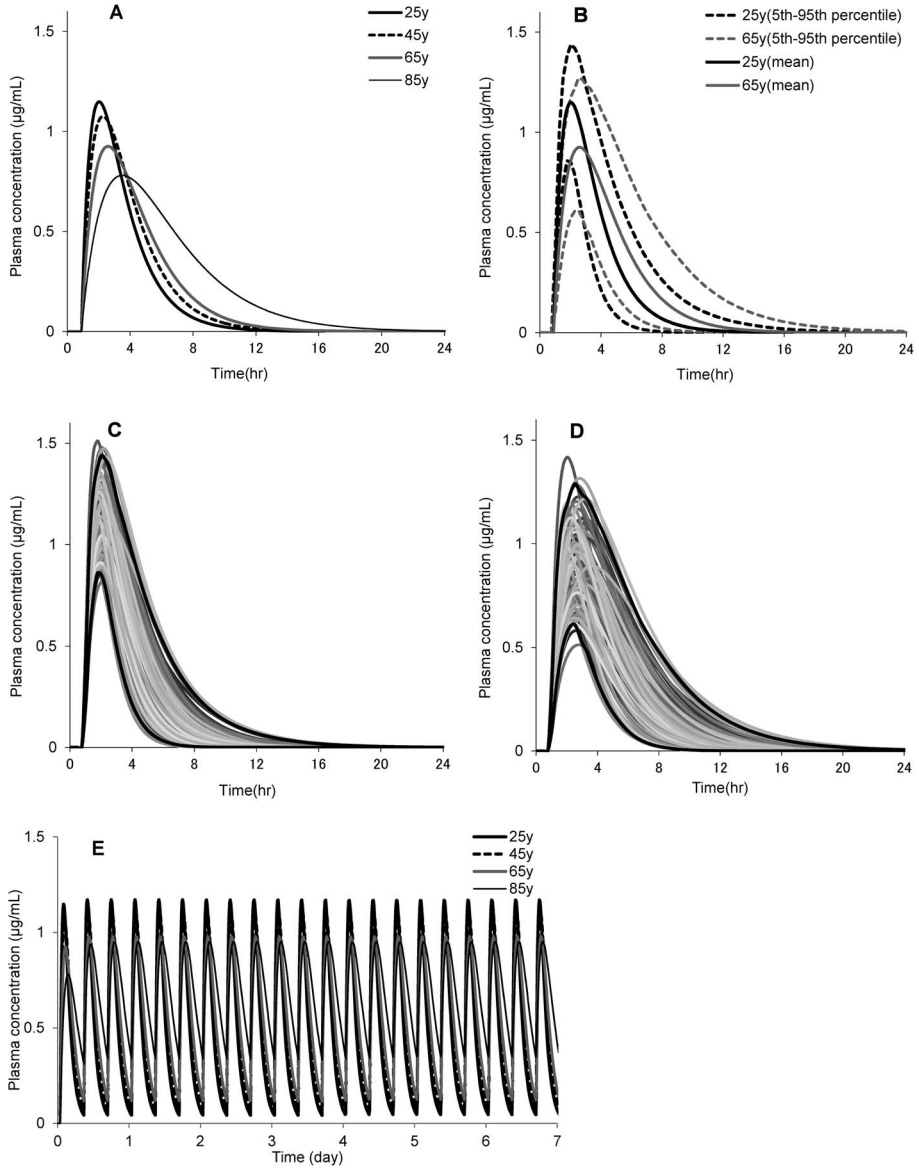
A; Single dose: 1.5 mg/kg (*ca.* 100 mg/man). Black bold solid line: Age: 25, WT: 70 kg, Ccr: 1.83 mL/min/kg. Black dashed line: Age: 45, WT: 70 kg, Ccr: 1.50 mL/min/kg. Gray bold solid line: Age: 65, WT: 70 kg, Ccr: 1.16 mL/min/kg. Black solid line: Age: 85, WT: 70 kg, Ccr: 0.83 mL/min/kg.

B; Single dose: 1.5 mg/kg (*ca.* 100 mg/man). Black bold solid line: Age: 25, WT: 70 kg, Ccr: 1.83 mL/min/kg. Black dashed line: 95% Confidence interval of plasma concentrations at 25 years old. Gray bold solid line: Age: 65, WT: 70 kg, Ccr: 1.16 mL/min/kg. Gray dashed line: 95% Confidence interval of plasma concentrations at 65 years old.

C; Single dose: 1.5 mg/kg (*ca.* 100 mg/man). Black bold solid line: 95% Confidence interval of plasma concentrations at 25 years old. Gray solid line: Plasma concentrations of simulated 100 subjects (Age: 25, WT: 70 kg, Ccr: 1.83 mL/min/kg).

D; Single dose: 1.5 mg/kg (*ca.* 100 mg/man). Black bold solid line: 95% Confidence interval of plasma concentrations at 65 years old. Gray solid line: Plasma concentrations of simulated 100 subjects (Age: 65, WT: 70 kg, Ccr: 1.16 mL/min/kg).

E; Repeated administration, 1.5 mg/kg (*ca.*100 mg/man) x 3 times/day. Black bold solid line: Age: 25, WT: 70 kg, Ccr: 1.83 mL/min/kg. Black dashed line: Age: 45, WT: 70 kg, Ccr: 1.50 mL/min/kg. Gray bold solid line: Age: 65, WT: 70 kg, Ccr: 1.16 mL/min/kg. Black solid line: Age: 85, WT: 70 kg, Ccr: 0.83 mL/min/kg.



tion is not largely involved in the renal excretion of CDTR, and instead active transport systems such as secretion play a role[27]. Actually, the results of clinical trial on CDTR-PI in concomitant use of probenecid suggested an involvement of secretion in the renal excretion of CDTR[11, 25]. That is, CL/F of CDTR is affected by the factor of age in adult subjects with normal renal functions, but the degree of such influence may be minor. On the other hand, in a clinical trial where the effect of age on pharmacokinetics was examined after oral administration of CDTR-PI, both $C_{max}$ and AUC of CDTR were reportedly increased with age[8, 28]. This is because the renal clearance (CLr) in the elderly subjects aged 65 or higher was 3.2 L/hr, which was 24% lower than 4.2 L/hr in young adult subjects aged between 25 and 40. This elderly subject group included those with renal dysfunction (personal communications), whose decrease in CL/F was so large that the impact of decreased CL/F on the increase in $C_{max}$ obviously exceeded the effect of age-dependent decrease in ka.

Next, Monte Carlo simulation was repeated 100 times on the basis of the plasma concentration profiles (Fig. 5-A) simulated from the population mean parameters in the subjects aged at 25 and 65 years as well as interindividual variability determined in population analysis. Fig. 5-B, C, D show the plasma concentration profiles and empirical 95% confidence interval of such 100 subjects. As a result, the plasma concentration profiles at both age groups largely overlapped with each other. The empirical 95% confidence interval for $C_{max}$ was 1.07～4.29 for the age of 25 and 0.40～3.88 for the age of 65. The empirical 95% confidence interval for AUC was 2.32～31.15 for the age of 25 and 2.37～41.22 for the age of 65, indicating the estimates were also largely overlapping with each other. This suggests that $C_{max}$ and AUC are likely to be affected by age; however the plasma concentrations of CDTR after oral administration of CDTR-PI in both age groups may be comparable when you consider interindividual variations. Accordingly, it was judged there would be no need of dosage adjustment depending on ages in oral administration of CDTR-PI to adult subjects with normal renal function based on the fact that CL/F of CDTR is not largely affected by the age as well as the interindividual variability of plasma concentrations.

## Conclusion

Population pharmacokinetic parameters of CDTR-PI were obtained using plasma CDTR concentrations for oral administration of CDTR-PI after meals to adult subjects.

Significant covariates for CDTR-PI ka, CL/F, Vd/F and Tlag were age, Ccr, WT and formulation (tablet or granule), respectively.

The ka decreased with age, CL/F increased with increasing Ccr and Vd/F decreased with increasing WT. In addition, the Tlag depends on formulation of CDTR-PI and the lag time in absorption of the tablet was longer than that of the granule.

As mentioned above, we could obtain the population mean parameters of CDTR-PI together

with interindividual variability and intraindividual residual variability after oral administration of CDTR-PI to adult subjects. In the future, this information will enable us to simulate the plasma concentrations of CDTR in subjects with various demographic backgrounds, which contributes to future examination of the efficacy and safety of CDTR-PI.

**Conflict of interest**

This work was sponsored by Meiji Seika Pharma Co., Ltd. Kayoko Matsumoto, Nobuo Sato, Nayu Mitomi, Yoshihisa Shitara and Shigeki Shibasaki are employees of Meiji Seika Pharma. The authors declare that they have no conflict of interest.

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