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Population pharmacokinetics of intravenous levofloxacin 500 mg/day dosage in infected patients

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The purpose of this study was to explore the population pharmacokinetic features of levofloxacin in Chinese infected patients. A total of 27 Chinese adult infected patients were treated with intravenous levofloxacin (500 mg/day). In total, 49 plasma samples of levofloxacin were collected immediately after intravenous dripping and before administration on the 3rd, 4th or 5th day. A nonlinear mixed effect model was used to model the population pharmacokinetic (PK) behavior of levofloxacin. The final population pharmacokinetic models were validated using the bootstrap method. Some covariates, including demographic characteristics and hematological and biological indicators, were analyzed. A structural model was developed based on a one-compartment model with intravenous infusion and first-order elimination. The typical population values for pharmacokinetic parameters of apparent clearance (CL) and apparent distribution volume (V) were 5.84 L/h and 43.3L, respectively. The inter-individual variabilities of CL and V were 7.75% and 6.4%, respectively, while the intra-individual variability of observed concentrations was 0.06 μg/mL. The covariates of age and AST influenced the CL and V values determined by the final model. The present study developed population pharmacokinetic models for levofloxacin in infected Chinese patients. The results detailed here could provide a reference for individualized levofloxacin therapy in the clinical setting.

1. Introduction

Frequently used in clinical practice, levofloxacin is the active L-isomer of the racemate ofloxacin, a fluoroquinolone with a broader spectrum of activity than older fluoroquinolones such as norfloxacin or ciprofloxacin (Geerdes-Fenge et al. 2000; Albarellos et al. 2005). *In vitro*, levofloxacin acts against a broad range of gram-negative (most Enterobacteriaceae) and gram-positive organisms (methicillin-susceptible strains of *Staphylococcus* spp. and *Streptococcus* spp.) as well as atypical and intracellular bacteria (*Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*). Its activity against anaerobic microorganisms is moderate (Fish and Chow 1997).

In treating human beings, levofloxacin is administered orally once a day. Its bioavailability is approximately 100% and is little affected by administration with food (Fish and Chow 1997). Oral absorption is very rapid and complete, with little difference in the serum concentration-time profiles following 500 mg oral or intravenous (infused over 60 min) doses. Levofloxacin can be maintained at high concentrations in lung tissues, most published studies have involved patients with lung infections. Steady-state intrapulmonary or bronchopulmonary levofloxacin concentrations are generally reported to be approximately 2- to 20-fold higher than plasma levofloxacin concentrations (Capitano et al. 2004; Boselli et al. 2005). The pharmacokinetic (PK) profiles of levofloxacin in healthy subjects and other healthy populations are well known (Sprandel et al. 2004; Overholser et al. 2005; Chow et al. 2001; Chien et al. 2005), and the PK features of this agent in patients with the pulmonary tuberculosis and urinary tract infections have been reported (Peloquin et al. 2008; Deguchi et al. 2010). However, there are limited data on the pharmacokinetics of levofloxacin in Chinese population, particularly in hospitalized Chinese infected patients.

For this study, patients with respiratory infections, digestive system infections, and urinary system infections were chosen as subjects for studying levofloxacin pharmacokinetics. The aims of the present study were to further explore the PK characteristics of levofloxacin treatment in infected patients and to establish population pharmacokinetic models to describe observed levofloxacin pharmacokinetics. The study also identified factors, such as age, body weight, liver function, and renal function, that were found to influence the pharmacokinetic variability of levofloxacin in the infected Chinese population studied. Throughout the study, doctors were provided with references regarding individualized levofloxacin administrations.

2. Investigations, results and discussion

2.1. Patient characteristics

The demographic and biological characteristics of the 27 final subjects are summarized in Table 1. The infected patients consisted of 13 males and 14 females, and 9 inpatients (33% of the total 27 patients) were older than 65 years.

Table 1: Demographic and biological characteristics of the infected patients

Characteristics	Means ± SD (Range)
Age, years	55.74 ± 17.36 (19–81)
Height, m	167.70 ± 5.90 (156–180)
Weight, kg	65.59 ± 11.47 (45–90)
Infusion time, h	1.96 ± 0.59 (1–4)
WBC, $\times 10^{-9}$/L	6.49 ± 4.78 (2.71–28.83)
N, %	60.94 ± 18.11 (20.60–94.30)
CRP, mg/dL	4.84 ± 7.61 (0.12–37.30)
ESR, mm/h	30.13 ± 18.76 (4–70)
GLU, mmol/L	5.42 ± 1.21 (4.02–9.11)
Cr, μmol/L	68.07 ± 14.06 (45.40–107.60)
Clcr, ml/min	105.4 ± 35.4(30.68–176.78)
BUN, mmol/L	6.05 ± 6.27 (1.33–36.80)
ALT, IU/L	26.37 ± 23.16 (5.01–100.30)
AST, IU/L	26.74 ± 19.22 (14–99.90)

Figures in parentheses indicate ranges. WBC = White Blood Cells; N:neutrophillic granulocyte. CRP = C-reactive protein; ESR = Erythrocyte Sedimentation Rate; GLU = Glucose; Cr = Creatinine; Clcr: Creatinine Clearance; BUN = Blood Urea Nitrogen; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase.

2.2. Drug concentration measurements

All blood levofloxacin concentrations were detected using HPLC and the internal standard method; 49 whole blood concentrations were available for population modeling.

The retention times of metronidazole (internal standard) and levofloxacin were 4.2 min and 8.3 min, respectively. The lowest detectable concentration was 0.5 $\mu g \cdot mL^{-1}$. The calibration curve was constructed in the range of expected concentration (0.1–20 μg/ml) in serum. Linearity was shown using a regression analysis of the calibration curves of levofloxacin generated a line with a correlation coefficient of 0.9990. Thus, the assay is linear for levofloxacin over the usable concentration range. The absolute recoveries of levofloxacin at three concentrations (0.1, 0.5, and 2.0 $\mu g \cdot mL^{-1}$) were 96.59%, 93.87%, and 85.58%, respectively. The method recoveries were 101.00%, 97.35%, and 103.35%, respectively. Inter-day RSDs corresponded to 8.73%, 2.35%, and 0.20%, respectively, while intra-day RSDs corresponded to 7.53%, 2.73%, and 0.34%, respectively.

2.3. Population pharmacokinetic model analysis

The structural model was a one-compartment model with first-order absorption and elimination. The pharmacokinetic parameters of levofloxacin estimated by NONMEM were clearance (CL) and distribution volume (V).

The interindividual variability model was ultimately evaluated using an exponential model, as shown in Eq. (1):

$$\theta_{ij} = \theta \times \exp(\eta_{ij}) \quad (1)$$

where θ_{ij} represents the *i*-th individual value of the parameter on the j-th occasion, θ represents the typical population value of the parameter, η represents the interindividual variability of the pharmacokinetic parameter and η is a random variables distribution with a mean of zero and variance of ω^2.

The residual error model was evaluated using the additive error model. The residual error model is shown in Eq. (2):

$$Y = IPRED + \varepsilon \quad (2)$$

where Y represents the observed concentration, IPRED represents the individual predicted concentration, which was simulated by POSTHOC with NONMEM, and ε is the residual error, which was randomly distributed with a mean of zero and variance of σ^2. The basic model pharmacokinetic parameter estimates were compiled in Table 2.

Table 2: Parameter estimates of the basic model

Parameter	Typical parameter estimate	SE%
CL, l/h	5.63	7.40
V, L	51.60	5.40
ωCL, %	10	26.90
ωV, %	8.17	18.80
σ, μg/ml	5.51	67.90

ω=interindividual variability; σ=intraindividual variability; SE% = percent standard error.

Table 3: Change in objective function values of covariate analyses

	OFV	ΔOFV	P value
Inclusion			
Basic model	78.12		
Influence of AST on V	63.47	−14.65	$P < 0.05$
Influence of age on CL	72.71	−5.42	$P < 0.05$
Elimination			
Full model	38.44		
Elimination AST	56.54	+ 18.10	$P < 0.01$
Elimination age	51.34	+ 12.90	$P < 0.01$

Table 4: Parameter estimates of final model and bootstrap validation

Parameter	estimate	SE%	Bootstrap	
			median	2.5^{th}, 97.5^{th} percentiles
CL, 1/h	5.84	7.20	5.88	4.92, 6.87
V, L	43.30	5.10	43.50	33.07, 51.84
θAGE	−0.06	32.30	–0.06	−0.11, −0.02
θAST	0.33	6.70	0.33	0.07, 0.53
ωCL, %	7.75	23.40	26.13	6.80, 32.20
ωV, %	6.40	19.40	24.60	5.70, 29.87
σ, μg/ml	0.06	29.70	0.08	0.03, 0.11

Six covariates were analyzed in the present study, and only the following covariates showed evidence of significantly influencing the pharmacokinetic parameters; age on CL and aspartate aminotransferase (AST) on V. Changes in the resulting objective function values were compiled in Table 3.

The final covariates' models were as follows.

$$CL = \theta_{CL} + (AGE - 50) \times \theta_{AGE} \quad (3)$$

$$V = \theta_v + AST \times \theta_{AST} \quad (4)$$

where θ_{cl} and θ_V are the typical population values of CL and V, respectively, and θ_{AGE} and θ_{AST} are coefficients of age and AST. The results of the final modeled pharmacokinetic parameters are presented in Table 4.

2.4. Model validation

Model validation is very important in population analyses (Brendel et al. 2007). The final models determined by the present

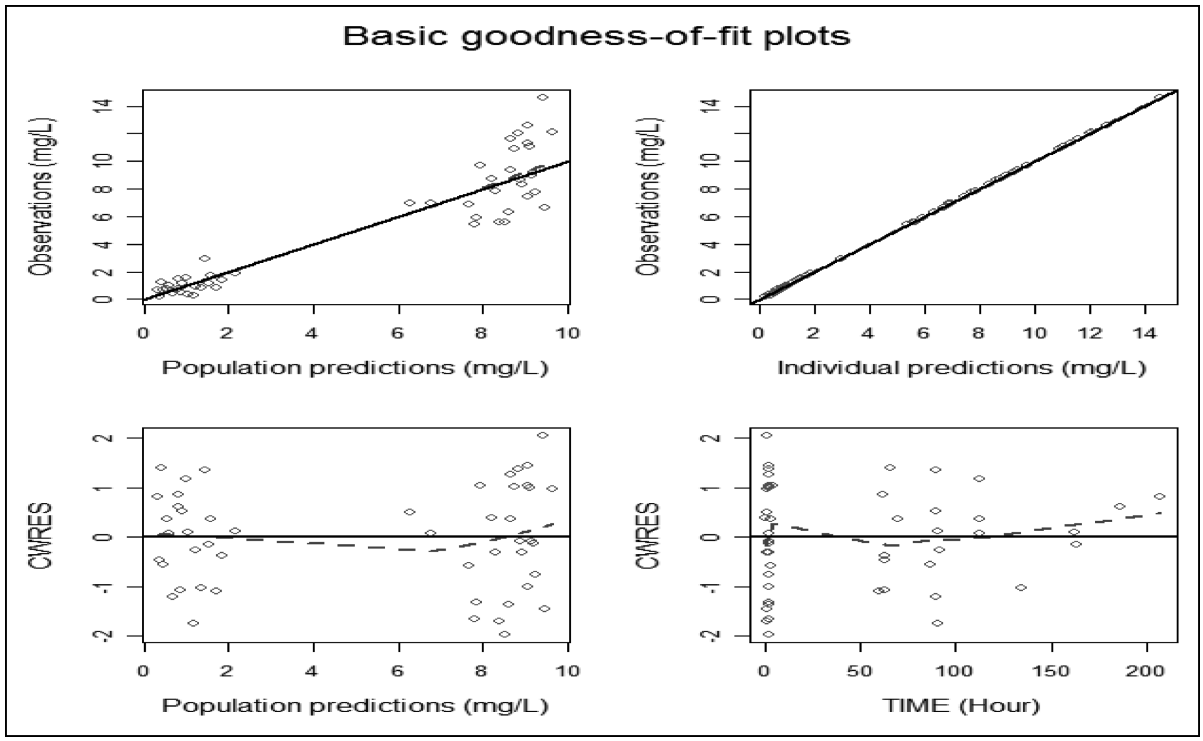

Fig. 1: Fit plots of the final model: observations versus population predictions (a) and observations versus individual predictions (b); conditional weighted residual versus populations (c) and conditional weighted residual versus time (d). The solid lines represent the lines of unity.

study were validated using bootstrap and VPC. The results of the bootstrap method, shown in Table 4, show that the median values of the parameters are close to the final model estimates. The goodness of fit of the final model is shown in Fig. 1; the scatter plot showed no major bias. The distributions of the simulated concentrations and observed concentrations versus time are shown in Fig. 2, where the distributions (50^{th}, 10^{th} and 90^{th} percentiles) of the simulated concentration-time curves are compared with observed concentrations. The final models accurately predicted the levofloxacin (500 mg/day) dosage in infected patients.

3. Discussion

Determining the pharmacokinetic profile(s) of a drug in an infected population is particularly important for determining medication dosages in clinical practice and for evaluating a new agent. The PPK study reported herein was conducted using clinical trials of levofloxacin to treat infection. We developed a PPK model for levofloxacin in Chinese patients with infections and described the PK characteristics of infected patients treated with levofloxacin (500 mg/day).

Previous studies (Fish and Chow 1997; Croom and Goa 2003) reported that levofloxacin pharmacokinetics were unaffected by

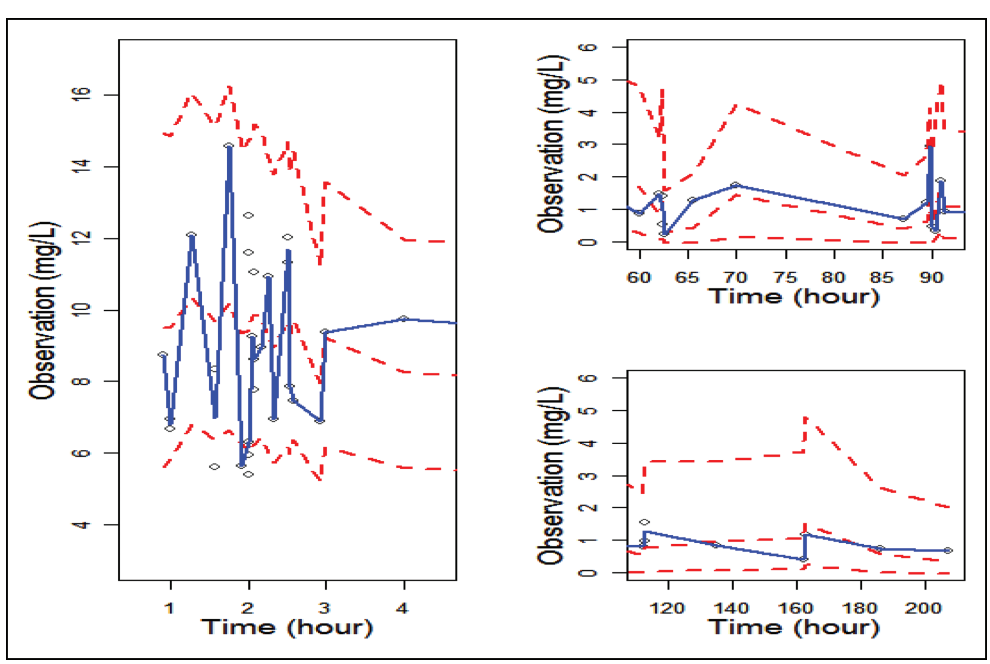

Fig. 2: VPC profile of the final model. The middle solid line represents the median of the simulated data. The lower and upper dashed lines are the 10^{th} and 90^{th} percentiles of the simulated data, respectively. Observations are shown as open circlec.

age, gender, height or race and that they did not differ between healthy adults and patients with serious infections (skin, respiratory tract, or urinary tract infections). In agreement with these previous reports, we found that gender, height and infected system had no significant influence on the final levofloxacin pharmacokinetic models. However, we found that age and AST significantly influenced levofloxacin pharmacokinetics. These conclusions differed slightly with results from a previous study that showed that Clcr and body weight significantly influenced CL and V, respectively. As discussed later, these different results may result from differences (between our patients and healthy subjects) in race, sample number, and age deviations.

In general, increases in age correlate with declined liver and kidney function (Thompson and Williams 1965). Our study found that age significantly influenced CL; greater ages correlated with lower CL levels. For a drug such as levofloxacin, which is predominantly cleared renally, older age and slightly higher average serum creatinine levels could be associated with glomerular filtration rates that are lower than those observed in healthy volunteers, causing decreased kidney CL levels and, therefore, decreased total CL resulting from levofloxacin treatment (Preston et al. 1998). Zhang et al. (2009) showed that patients with mild renal dysfunction (50 ml/min < CL_{cr} < 80 ml/min) had 34% higher $AUC_{0–24}$ values compared to patients with normal renal function (CL_{cr} > 80 ml/min). Other studies (Chien et al. 2005; Peloquin et al. 2008) also reported higher $AUC_{0–24}$ values in elderly patients (>65 years) compared to younger patients. This change in $AUC_{0–24h}$ was thought to be derived from declining renal function in the elderly. Consistent with our results, Tanigawara et al. (1995) also reported age, particularly > 65 years, and corresponding renal function were factors affecting the clearance of levofloxacin. These results have therapeutic implications in that patients with higher CLcr values will have lower AUC values and, consequently, lower probabilities of successful outcomes (Preston et al. 1998). In contrast, the old patients or the patients with lower CLcr values will have higher AUC values and lower CL values, and consequently, are more likely to suffer from toxicity reactions under levofloxacin.

Levofloxacin exhibits approximately 24–38% binding to serum plasma proteins (primarily albumin). This serum protein binding is independent of serum drug concentrations (Eliopoulos et al. 1996). The drug is widely distributed throughout the body and penetrates well into most body tissues and fluids. Drug concentrations in tissues and fluids are generally greater than those observed in plasma, such as lung tissue. Previous clinical studies have demonstrated that following oral and IV dosing, levofloxacin is widely distributed throughout the body, with tissue concentrations often exceeding serum concentrations (Von Baum et al. 2001a, 2001b). Our study concluded that AST, an indicator of liver function, significantly influenced V. However, Cheng et al. (2002) reported that the AUCs of levofloxacin in blood and bile were 237.9 ± 24.1 and 88.7 ± 14.1 μg/ml·min, respectively, suggesting that levofloxacin may be excreted from the blood to the bile. The distribution of levofloxacin in blood and bile fluids indicated that levofloxacin undergoes hepatobiliary excretion and that there is rapid exchange and equilibration between the blood and hepatobiliary systems. The drug is primarily eliminated *via* the kidneys, and approximately 80% of levofloxacin is eliminated, unchanged from the initial form administered, in urine through glomerular filtration and tubular secretion. Swoboda et al. (2003) also demonstrated high levofloxacin drug levels in the biliary fluid. Combined with our final model, these previously published studies indicate that liver function can influence V values (in levofloxacin pharmacokinetics). When administered at a dosage of 500 mg/day to infected patients with higher AST of hepatic dysfunction, levofloxacin can certainly be distributed in bile and has higher V values, which can influence its distribution in serum.

In conclusion, in the present study, the population pharmacokinetics of levofloxacin were studied in 27 inpatients, and population pharmacokinetic models were developed. The following covariates were found to influence the final models: Age on CL, and AST on V. Our results could be used as a reference for individualized levofloxacin therapy in the clinical setting.

4. Experimental

4.1. Subjects

This prospective, randomized study was conducted from May 2010 to September 2011 among inpatients of Tianjin First Center Hospital in China. The study was approved by the Institutional Review Board of Tianjin First Hospital, Tianjin, China. Informed, verbal consent was obtained from the patients or their caregivers for blood sampling as well as routine therapeutic drug monitoring.

After being diagnosed with specific infectious diseases (see above) and validated for treatment with levofloxacin, all subjects, irrespective of body weight, sex, and age, were treated with standard 500 mg/day intravenous dosages of levofloxacin. After strict screening with regard to inclusion and exclusion criteria, 27 inpatients were finally enrolled in the study.

The inclusion criteria for the pharmacokinetic study were as follows: (1) the infections in respiratory, digestive and/or urinary systems were accurately diagnosed; (2) the disease was validated for levofloxacin treatment; (3) levofloxacin was applied as the only anti-infection therapeutic drug; (4) the course of drug administration was between 3 and 14 days; (5) complete information for each subject was recorded during the course of drug administration.

The exclusion criteria for the study were as follows: (1) anti-infection treatment with levofloxacin was terminated for non-therapeutic reasons; (2) other antibiotics were applied simultaneously; (3) a drug affecting the disposition of levofloxacin was applied; (4) patients underwent surgical intervention during anti-infection treatment; (5) patient information was incomplete.

4.2. Drug administration and sampling

All patients in this study were intravenously administered 500 mg of levofloxacin (injection, 100 ml: 500 mg) once daily. Blood samples were drawn twice and were deposited in heparinized tubes both immediately after the first intravenous dripping and before application on day 4 (range, day 3 to 5) of the treatment period. The exact times of administration and blood sampling were recorded. The blood samples were centrifuged for 10 min at 3500 rpm. The plasma samples were collected and stored at -20 °C until analysis.

4.3. Concentration measurements

Plasma levofloxacin concentrations were analyzed using high-performance liquid chromatography (HPLC) with ultraviolet detection (294 nm) via a method validated in our laboratory.

The content of levofloxacin in each sample was determined using a Kromasil C18 (150 mm × 4.6 mm, 5 μm) column with a fixed sample injection volume of 10 μL. The mobile phase was 0.05 mol L^{-1} potassium dihydrogen phosphate solution (pH adjusted to 3.1 using phosphoric acid) – acetonitrile (85:15, V:V) at a flow rate of 1.0 mL·min^{-1}. The UV detection wavelength was set at 294 nm; the column temperature was the same as the room temperature, and metronidazole was chosen as the internal standard.

4.4. Population pharmacokinetic model analysis

Population pharmacokinetic analyses were performed using NONMEM (Version VI, level 1.1, Globomax Corp., MD, USA). All parameters were estimated using the first-order conditional estimation method with interaction (FOCE-1). A one-compartment model incorporating a first-order absorption process (subroutines ADVAN1 and TRANS2 in the PREDPP library) was used to simulate levofloxacin population pharmacokinetic data.

4.5. Structural Model

4.5.1. Random effect model

Interindividual variability models pertaining to the levofloxacin pharmacokinetic parameters were evaluated using additive, proportional and exponential models. The residual error model was also tested using additive, proportional and combined (proportion plus additive) models.

4.5.2. Covariate model

Model selection was based on comparisons of each model's precision of parameters' estimates, goodness of fit and minimum value of the NONMEM objective function value [-2log(likelihood)]. Covariates were initially screened using scatter plots of individual pharmacokinetic parameters versus demographic and biological characteristics and by generalized additive modeling using SAS 9.1.

The potential covariates that were screened by generalized additive modeling were individually introduced into the basic model and screened again with NONMEM. The effects of covariates were assessed by χ^2 testing of the difference between the OFV of the basic model and that of the incorporated covariate model. When a covariate was incorporated, a decrease in $\Delta OFV > 3.84$ (degree of freedom, d.f. = 1) was considered significant at α=0.05; potentially significant covariates were also screened.

The final regression model was established by applying step-wise backward elimination to the full regression model. When a covariate was removed, a change of $\Delta OFV > 6.64$ (d.f. = 1) was considered significant at α=0.01.

Some covariates, including demographic characteristics and hematological and biological indices, were analyzed using stepwise forward inclusion and backward elimination. The covariates were divided into continuous and dichotomous variables. Additive, exponential and power models were tested for continuous variables, while power models were evaluated for dichotomous variables.

4.6. Model validation

The validity of the population pharmacokinetic model was assessed by basic goodness-of-fit plots, including observed concentrations (OBS) versus individual predictions (IPRED), observed concentrations (OBS) versus population predictions (PRED) and conditional weighted residuals (CWRES) versus population predictions (PRED) and time.

The accuracy and robustness of the final model were simultaneously evaluated using the bootstrap and visual predictive check (VPC) resampling techniques.

Using the Wings for NONMEM program, 500 nonparametric bootstrap replicates (see Ette et al. 2003; Shi et al. 2011 for details) were assessed. Bootstrap results for which the minimizations were successful and covariances were acceptable were further analyzed. The medians and 2.5–97.5 percentiles of the bootstrap data-set parameters were compared to the final pharmacokinetic parameter estimates.

The rationale of VPC is to simulate a new data set according to the final model parameters and, subsequently, to fit this new data set with the final model, thereby determining the parameters for the new data set. Plots of the observed concentrations and 90% prediction intervals of simulated concentrations versus time were obtained with the assistance of R for NONMEM and Wing for NONMEM.

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