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Pharmacokinetics of 17-hydroxyprogesterone caproate in multifetal gestation

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Abstract

Objective—To define the pharmacokinetic (PK) parameters of 17-hydroxyprogesterone caproate (17-OHPC) in multifetal gestation.

Study Design—Blood was obtained at 24–28 weeks and at 32–35 weeks in 97 women with twin and 26 women with triplet gestation receiving 17-OHPC. Six of the women with twins had daily blood sampling for 7 days between 24 and 28 weeks and PK parameters were estimated using noncompartmental analysis. Modeling was applied to estimate the population parameters and to simulate various treatment scenarios.

Results—The apparent half-life of 17-OHPC was 10 days. BMI significantly impacted 17-OHPC concentrations but fetal number and parity did not. Apparent clearance was significantly greater in African American than in Caucasian women ($p = 0.025$).

Conclusions—This is the first pharmacokinetic analysis of 17-OHPC in pregnant women. Determination of half life, covariates affecting plasma 17-OHPC concentrations and modeling of drug behavior provide insights into this drug's pharmacology during multifetal pregnancy.

Keywords

17-hydroxyprogesterone caproate; pharmacokinetics; multifetal pregnancy

Introduction

17-hydroxyprogesterone caproate (17-OHPC) reduces the rate of recurrent preterm birth in women carrying a single fetus. This therapy has been evaluated in other conditions associated with preterm birth including multifetal gestation,^{2,3,4} short cervix,^{5,6} and cervical cerclage.⁷ Despite widespread clinical use, no data exist describing the pharmacokinetics of 17-OHPC in pregnancy or the plasma concentrations achieved during therapy for preterm birth prevention. In the current study, we evaluated the pharmacokinetics (PK) of 17-OHPC in women with either a twin or triplet gestation who were receiving 17-OHPC in one of two separate placebo controlled trials aimed at determining the utility of this agent in reducing preterm birth.^{2,3} We also used population pharmacokinetic modeling to simulate plasma 17-OHPC concentrations under various clinical conditions.

MATERIALS AND METHODS

Patients and Drug administration

A total of 661 women with twins and 134 women with triplet gestation were recruited into two randomized controlled trials.^{2,3} Subjects received weekly injections of either 250 mg 17-OHPC in 1 ml castor oil or 1 ml castor oil alone from the time of enrollment (16 0/7

weeks – 20 6/7 weeks) until 35 weeks unless delivered earlier. Data recorded for each patient included maternal age, parity, race, BMI and gestational age at enrollment, as well as gestational age at each blood sampling and at delivery. These data were evaluated as covariates in the pharmacokinetic analysis. This study was approved by the institutional review boards of each clinical site and of the data coordinating center. Consent was given before enrollment into the study. The parent trials were registered at Clinical Trials.gov (NCT00099164).^{2,3}

Pharmacokinetic sampling schedule

Among subjects recruited for the primary randomized controlled trials and receiving all their scheduled injections of 17-OHPC, 97 with twins and 53 with triplets were undelivered and had a single blood sample drawn between 24–28 weeks (epoch1) for measurement of 17-OHPC concentration. Among these women, 70 with twins and 26 with triplets were undelivered and had a second sample taken at 32–35 weeks (epoch 2) for analysis. The infrequent (sparse) sampling described above is useful in comparing plasma 17-OHPC concentrations over time and between groups but does not lend itself to classic pharmacokinetic analysis which requires frequent sampling during one dosing interval. Fifteen of the 97 women with twins agreed to have a single blood sample taken daily for seven consecutive days over a dosing interval of one week between 24–28 weeks (intensive sampling). The first blood sample was drawn minutes prior to a scheduled injection. Recruitment of these 15 women was masked to treatment arm; therefore women who received either 17-OHPC or placebo were included. All of the fifteen women had received a minimum of four weekly injections of 17-OHPC from the time of enrollment in anticipation that steady state concentration in those women receiving 17-OHPC would be achieved by the start of the PK study. Analysis of these plasma samples was not undertaken until completion of the clinical trials so that masking of treatment arm was maintained

Sample Analysis

For all 17-OHPC measurements, blood was collected in 10 ml tubes with EDTA as the anticoagulant and centrifuged within one hour at $3500 \times g$ for 10 minutes. The supernatant plasma was aliquoted to 1 ml tubes and frozen at -70 degrees centigrade until analyzed by high performance liquid chromatography with tandem mass spectrometry (LC-MS). The assay methodology has been reported.⁸ The lower limit of detection of the assay for 17-OHPC was 1 ng/ml, inter and intra assay variability at 10 ng/ml were 7.9 and 5.2%, respectively. The analyst and the clinical centers involved in recruitment remained masked to the treatment assignment until the analyses were completed.

Noncompartmental Pharmacokinetic Analysis

Nine of the 15 subjects who underwent “intensive sampling” (daily for seven days) had received placebo and were therefore not included in the pharmacokinetic analysis though their plasma samples had been analyzed. Pharmacokinetic parameters for the 6 subjects who received 17-OHPC and underwent “intensive sampling” were estimated using the standard noncompartmental approach implemented in WinNonlin® (v. 4.0, Pharsight Corp., Mountain View, CA). Trough concentrations (C_{trough}) maximum concentration (C_{max}) and time to maximum concentration (T_{max}) were determined from the observed data. The elimination rate constant (λ_z) was determined by log-linear regression of the terminal linear disposition phase. Half-life ($t_{1/2}$) was estimated by $0.693/\lambda_z$. Area under curve (AUC) was calculated using the linear trapezoidal method. Apparent clearance [clearance (CL)/bioavailability (F)] was estimated by $Dose/(AUC)$, and the apparent volume of distribution (VD/F) was calculated by $Dose/(\lambda_z AUC_{inf})$.

Population Pharmacokinetic Analysis

Population pharmacokinetics is the pharmacokinetic evaluation of patients who are representative of the target patient population being treated with a medication. This methodology is commonly used to define patient specific factors such as weight, race or sex that contribute to the variability in drug concentrations. Large populations of subjects with fewer samples taken from each subject can be analyzed with this methodology. With a sufficiently large population, estimates of the impact of covariates on pharmacokinetic parameters can be made without having to collect numerous samples from each subject. For the current study, analysis was performed by means of non-linear mixed effects modeling implemented in the Monolix® software. Both sparsely sampled and intensively sampled data used in the non-compartmental analysis were included in the dataset.

Preliminary analysis for the structural model was performed by comparing one-compartment model with two and three compartment models. A proportional error model was used for describing residual variability. Interindividual variability was assumed to have a log-normal distribution. The patient characteristics BMI, race, fetal number, and parity were evaluated as covariates during the model building process as described by Lavielle and Mentre.⁹ The goodness of fit of the final model was evaluated by inspecting the following charts: scatterplots of predictions (population and individual) versus individual observations; population weighted residuals versus predictions and independent variable (time); absolute individual weighted residuals versus individual predictions. In addition, model validation was performed using prediction distribution errors and visual predictive check, obtained by conducting 1000 Monte Carlo simulations of the data set for the final model.^{9,10}

Further, simulations were carried out based on the final model to evaluate the effect of changes in BMI and dosing regimen on the plasma concentration time profiles of 17-OHPC.

Statistical Analysis

GraphPad Prism (4.01) was used for performing the statistical tests for significance. Non-parametric (Mann Whitney U) tests were used for group comparisons. Kruskal-Wallis test with Dunn's multiple comparison was used for testing equality of population medians in multiple groups. We considered p-values < 0.05 to be significant.

RESULTS

Pharmacokinetics (Intensive Sampling)

As expected, among the women who agreed to intensive (daily) sampling, 17-OHPC was not detectable in the plasma of the 9 women who received placebo but was detectable in all six women who had received 17-OHPC. Figure 1 depicts the mean ($\pm$ SD) plasma concentration of 17-OHPC in the six women with twins who had daily blood sampling over a 7 day period. Average peak concentration (C_{max}) of 17.3 ng/ml was noted at the first post injection sample at 1 day. Over the ensuing 6 days, plasma concentrations declined slowly to a nadir of 9.7 ng/ml at 7 days post injection. Selected pharmacokinetic parameters (mean, SD and range) for 17-OHPC in these 6 subjects are summarized in Table 1. The apparent half life was long at 10 days suggesting slow release from either the castor oil depots or maternal fat. The wide range of AUC and C_{max} values indicates considerable inter-individual variation in absorption and metabolism of 17-OHPC. The peak concentration (C_{max}) occurred 1.2 days (T_{max}) after the injection. The apparent volume of distribution was large with considerable inter-individual variation. Apparent clearance varied two-fold with a mean of 1204 l/day.

Steady State Concentration

We also evaluated whether steady state concentrations of 17-OHPC were achieved over the course of therapy (Figure 2). For this analysis only women who received all their scheduled injections and remained undelivered through epoch 2 (32–35 weeks) were included. This included 70 women with twins and 12 women with triplets. Among these women, the mean plasma concentrations of 17-OHPC were higher in epoch 2 than in epoch 1 for both the twin and triplet groups and significantly so in the twin group ($p=0.002$). The mean time from first injection to first blood draw was 43.2 (sd 12.5) days for twins and 45.0 (sd 12.0) days for triplets. The mean time between first and second blood draw was 46.1 (sd 8.2) days for twins and 44.3 (sd 5.8) days in women with triplets. Since plasma concentrations at epoch 2 (32–35 weeks) were higher than at epoch 1 (24–28 weeks) steady state concentrations were not achieved by epoch 1.

Impact of BMI and other covariates on 17-OHPC concentrations

We evaluated the impact of pre-pregnancy BMI, race and parity on plasma 17-OHPC concentrations only in women with twins. In this cohort we evaluated separately the 97 women who had received all their scheduled injections of 17-OHPC and remained undelivered until the first blood sample was drawn between 24–28 weeks gestation (epoch 1) and the 70 women who received all their scheduled injections and remained undelivered at the second blood draw at 32 – 35 weeks (epoch 2). A significant, ($p<0.01$) albeit weak linear relationship ($r=-0.28$ for epoch 1 and -0.33 for epoch 2) was observed for plasma 17-OHPC and BMI in women with twins (data not shown). Plasma concentrations of 17-OHPC in African Americans (AA) in epoch 2 only were lower ($p=0.051$) compared with Caucasians (CA). Parity did not impact plasma 17-OHPC concentrations significantly in either epoch.

Impact of Fetal Number of 17-OHPC Concentration

Concentrations of 17-OHPC (mean and median) did not differ significantly in women carrying triplets compared with women carrying twins. This applied to both sample time points (Figure 2).

Population Pharmacokinetics (POP-PK)

A total of seventy-one patients with twin gestation (65 in the sparsely sampled group and 6 in the intensively sampled group) who had at least two samples drawn during the study were included in the POP-PK model building process. A total of 188 observational data points were collected and utilized for this analysis. The data was best described by a one-compartment model with first order absorption. Of the various covariates tested in building the final model, BMI was observed to have a significant effect on the estimation of 17-OHPC clearance and was included in the final model. Although race was not a significant covariate in the final model, plasma clearance in African Americans was significantly higher than in Caucasians ($p<0.05$) (Fig.3).

The estimates of the pharmacokinetic parameters for these 71 subjects and their respective standard errors are shown in Table 2. The inter-individual variability (IIV) was observed to be ~24% for clearance and ~49 % for volume of distribution. The correlation coefficients between predicted vs observed concentrations of 17-OHPC for individual and population estimates were 0.85 and 0.50, respectively. This indicates the model fit to be fairly good for each individual subject data. The observed variability in plasma concentrations between subjects was reduced when adjusted for covariates, but other variables not collected in the study also could have contributed to the additional variability in plasma concentrations.

Plasma Concentration Simulations

We utilized pharmacokinetic parameters obtained by POP PK analysis to simulate plasma 17-OHPC concentrations under various clinical scenarios. Simulations were carried out to explore the effect of changes in BMI and dosing regimen on the plasma concentration time profiles of 17-OHPC (Figure 4). The plasma concentration of 17-OHPC varied significantly with BMI (Figure 4a) showing a more than two-fold difference in concentration over the BMI range seen in our subjects (18–45 kg/m²).

The impact of a loading dose on time needed to reach steady state concentrations was also evaluated. A simulated loading dose of 1000 mg reached and maintained steady state within one week (Figure 4b). The final simulated steady state concentrations achieved with a loading dose of 1000 mg followed by weekly injections of 250 mg would be comparable to those observed without a loading dose. We also evaluated the effect of changing the dosing schedule on the concentration-time profile (Figure 4c). Administering a dose of 500 mg once every 2 weeks achieved predicted steady state concentrations similar to those with a 250 mg weekly injection although peaks were about 15% higher and trough concentrations were about 15% lower with the 500 mg dose.

Comment

This is the first report of plasma concentrations and pharmacokinetic analysis of 17-OHPC in pregnant women.¹¹ Only one other study has evaluated the pharmacokinetics of 17-OHPC but that was in non-pregnant women.¹² Pharmacokinetic evaluation has not been reported in pregnant women with singleton gestation receiving 17-OHPC, so this study in women with multifetal gestations provides an opportunity to evaluate this medication in pregnancy. Our data provide insight into the general pharmacological properties of this agent. We have shown that the half-life of 17-OHPC is long, that plasma concentrations are affected by maternal BMI but not by fetal number or parity. We also demonstrated higher clearance and lower concentrations of the drug in African American compared with Caucasian women. We have simulated plasma 17-OHPC concentrations and have demonstrated how maternal BMI would affect plasma concentrations and how alternative dosing regimens would affect targeted plasma concentrations.

The half life of 17-OHPC in twins was long at 10 days. This long half life coupled with our demonstration that 17-OHPC is rapidly metabolized in vitro by human hepatocytes and liver microsomes¹³ suggests that slow release from the castor oil depot or maternal body fat determines terminal half-life of 17-OHPC rather than the drug's metabolism or elimination characteristics. A long half life is also seen in non-pregnant women and can be expected in pregnant women with singleton gestation.

The time to achieve peak concentration of 17-OHPC was 3–7 days in non-pregnant women¹², whereas we noted peak concentrations at 1–2 days after an injection. We did not sample prior to the 24 hours time point so it is possible that in women with twins, the peak plasma concentrations after an intramuscular injection occurs before 24 hours in women carrying twins. Nonetheless, it appears that the time to peak concentration after an intramuscular injection is shorter in pregnant women than in non-pregnant women. This finding is not unexpected as blood flow to most tissues in pregnancy is increased compared with that in non-pregnant subjects. The rate of rise in plasma 17-OHPC concentrations is slow compared with intramuscular injections of other drugs dissolved in water based solvents.¹⁴ The castor oil solvent slowly releases the 17-OHPC. The time to rapidly achieve the desired concentration would become more relevant if other indications requiring a rapid onset of action of 17-OHPC are evaluated in clinical trials (eg treatment of preterm labor).

We selected to obtain blood samples at two time points. The first at 24–28 weeks was selected in anticipation that steady state would have been reached since women began their injections between 16–20 weeks gestation. The second sample was obtained at 32–35 weeks to evaluate whether the drug accumulated with repeated injections. Steady state concentration however, was not achieved by the time of the first blood draw. The reason steady state is not achieved is likely due to the continuous, slow release of 17-OHPC from the castor oil depots which is augmented with each injection. The therapeutic concentration for 17-OHPC has not been established, but once it is, a loading dose could be administered if therapeutic concentrations need to be rapidly achieved.

In this study, the pharmacokinetic parameters calculated from compartmental analysis were used to simulate 17-OHPC plasma concentration time profiles under multiple hypothetical clinical scenarios. The simulations were based on pharmacokinetic parameters estimated from population pharmacokinetic analysis and included all the samples (trough concentrations and PK samples) and so are not constrained by the potential error in any half life estimates based on the pharmacokinetic study. The simulations we performed from women with twin gestation are useful in providing a perspective of the drug's behavior in pregnancy. With modeling, we were able to demonstrate a significant impact of BMI and race on plasma 17-OHPC concentrations. The basis for these differences is unclear but the racial differences in 17-OHPC clearance suggest the possibility that genetic factors may influence 17-OHPC pharmacologic behavior. Once therapeutic concentrations of 17-OHPC are determined, higher doses may be needed to achieve desired concentrations in obese women and in African-American women to achieve desired concentrations.

Simulations were also conducted to determine other possible dosing strategies. For example, we demonstrated that a dosing schedule of 500 mg administered once every two weeks could be utilized to achieve plasma concentrations comparable to those achieved with the currently utilized regimen of 250 mg weekly. This regimen would clearly improve patient's acceptability. However, this dosing schedule needs to be evaluated carefully since the peak/trough fluctuations were greater in this case as compared to the 250 mg/week regimen. Furthermore, these simulation data cannot be applied to women with a singleton gestation. We also demonstrated with our simulations that, if there was clinical need to achieve target steady state concentrations rapidly, this could be done with a loading dose. The issue of safety of such an approach would require consideration.

Conclusions regarding 17-OHPC pharmacokinetics reached in women with multifetal gestations may not be applicable to women with singleton gestations. However, the findings in women with a twin or triplet gestation provide a basis for evaluating the impact of covariates on the pharmacology of 17-OHPC in singleton gestations. Similar simulations with ritodrine proved useful in defining the association between drug dose and side effects and in demonstrating the harmful effects of rapid dose escalation.¹⁵

17-hydroxyprogesterone caproate is recommended as a treatment option for women with a prior preterm birth.¹⁶ Vaginal progestins have not proven consistently effective in this population¹⁷ so 17-OHPC continues to be the therapeutic option of proven benefit for this indication.¹ Despite the widespread use of this agent, very little pharmacologic information exists as to the proper dosing regimen or the mechanism of action of the drug.^{18,19, 20, 21, 22, 23} The currently utilized regimen of 250 mg injected intramuscularly weekly is empiric. Our study indicates a wide inter-individual variation in the pharmacology of 17-OHPC. Such wide variability suggests that the beneficial effect of 17-OHPC in reducing preterm birth rates in singleton gestation may be further optimized with a drug administration regimen that achieves the desired concentration.

In conclusion, this is the first report of plasma concentrations of 17-hydroxyprogesterone caproate in pregnant women. This report defines the pharmacokinetic behavior of 17-hydroxyprogesterone caproate in women with twin gestation and the impact of BMI, race and fetal number on plasma 17-OHPC concentrations. Whether substantive differences in these observations will be seen in singleton gestation requires additional study.

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DEFINITIONS

Pharmacokinetics

This term describes the time course of a drug in the body and includes absorption , distribution, metabolism and elimination.

	In simple terms it is what the body does to an administered drug.
Pharmacodynamics	This describes the relationship between the pharmacological response and the drug concentration. This includes physiologic or biochemical effects of drugs on the body or on microorganisms or parasites within or on the body.
Sparse sampling	A technique by which a limited number of samples is obtained from a large population of subjects taking the same medication in order to make inferences about the drug or its response.
Intensive sampling	This is typically done within a dosing interval in order to characterize the pharmacokinetics of a drug in a given patient
One compartment model	If a drug distributes instantaneously through out the entire body it is said to exhibit a one compartment model.
Multi compartment model	If a drug does not distribute instantaneously through out the entire body it is said to exhibit a multi compartment model. Under such a condition while the drug distributes instantaneously to certain parts of the body, it takes a longer time to reach other parts of the body.
Steady state concentration	Steady state concentrations of a drug are achieved when the rate at which a drug comes into the body equals the rate at which the drug leaves the body. At steady state, the plasma concentration of a drug is constant during continuous intravenous infusion, or the plasma concentration versus time profile during a dosing interval is identical to the plasma concentration versus time profile during the subsequent dosing intervals for a fixed dose and dosing frequency. Steady state plasma concentrations are achieved in approximately 5–6 half lives.
C max	This is the highest concentration of a drug in blood or plasma during a dosing interval after administration of a drug.
Tmax or T peak	This is the time at which maximum blood or plasma concentrations are achieved during a dosing interval.
Area under the concentration –time curve	This is the area under the blood or plasma concentration versus time curve for a drug.
Clearance	This describes the over all ability of the body to clear the drug. It is the volume of blood or plasma that is completely cleared of the drug per unit time. The clearance is calculated as the amount of drug cleared (for IV dose this will be dose) divided by the area under the blood or plasma concentration versus time.
Volume of distribution	Volume of distribution is a hypothetical volume that relates the concentration of the drug in the measured biological fluid (normally plasma or serum or blood) to the amount of drug in the body. In other word, it is the apparent volume into which the drug has to be distributed at a concentration equal to the

concentration measured in the biological fluid. It is typically expressed in liters or in liters per kilogram. This parameter provides information about the extent to which the drug is distributed outside the vascular system.

Apparent Half-life

This is a measure of the time that it takes for the drug concentration to decrease from a given value to one half of its value. It takes about 5–6 half lives for most of the drug to be out of the body. It takes about 5–6 half lives to reach steady state.

Simulation of plasma concentrations

This is an approach that utilizes the pharmacokinetic parameters of a drug and mathematical modeling to predict the blood or plasma concentration versus time for various doses and dosing frequencies.

Monte Carlo simulations

A problem solving technique used to approximate the probability of certain outcomes by running multiple trial runs, called simulations, using random variables.

Population pharmacokinetics (POP – PK)

This describes the relationship between physiology and pharmacokinetics and pharmacodynamics. Population pharmacokinetics is the study of the sources and correlates of variability in drug concentrations in the patient population receiving clinically relevant doses of a drug of interest.

Figure 1. Mean Plasma Concentration of 17-OHPC Following IM Injection of 250mg
17-OHPC concentration–time profiles for 6 subjects with twins who had sampling done before and then daily for seven days after an injection. Values are mean ($\pm$) standard deviation.

Figure 2. Mean Plasma Concentrations of 17-OHPC in Twin and Triplet Gestation During Two Gestational Epochs

Mean ($\pm$ sd) 17-OHPC concentrations in the 70 subjects with twins and the 12 subjects with triplets who had blood obtained during epoch 1 at 24–28 weeks and epoch 2 at 32–35 weeks. Single asterisk indicates significant difference ($p < 0.002$) between epoch 1 and epoch 2 in twins. Concentrations in twins vs triplets were statistically similar ($p > 0.05$) both in epoch 1 and 2. Mann-Whitney test was used for the comparisons.

Figure 3. 17-OHPC Clearance According to Race

A boxplot depicting the median 17-OHPC clearance (individual) estimates associated with different ethnicities. The bars represent 25th (lower bar) and 75th (upper bar) percentile. AA – African Americans (n=14), CA – Caucasians (n=46) and HIS – Hispanics (n=9). The mean clearance in the Caucasians was significantly lower than that of African Americans ($p < 0.05$). The individual estimates were obtained with the final model which included BMI as the covariate. Kruskal-Wallis one-way analysis of variance with Dunn's post test was used for the comparison.

Figure 4. Simulated Plasma 17-OHPC Concentrations

Simulated plasma concentration time profiles of 17-OHPC in pregnant subjects. The bold indicates the simulated plasma concentration utilizing a dose of 250 mg IM once weekly of 17-OHPC. The lighter line indicates simulated concentrations under various scenarios.

- a. effect of BMI (18, 45 and 27) on plasma concentration time profiles,
- b. effect of adding a loading dose of 1000 mg to the currently recommended regimen, and
- c. effect of changing the dosing schedule from 250 mg once weekly to 500 mg every 2 weeks.

TABLE 1

Pharmacokinetic Parameters of 17-OHPC in Women with Twin Gestation

C _{trough} (ng/ml) (range)	C _{MAX} (ng/ml) (range)	T _{MAX} (Days) (range)	t _{1/2} (days) (range)	AUC ^{0-t} (ng/ml/day) (range)	Cl/F (l/day) (range)	V _d /F (L) (range)
11.17 ± 4.6 (4.8 – 16.3)	17.3 ± 6.7 (12–27)	1.2 ± 0.41 (1–2)	10 ± 4.0 (6–16)	86.1 ± 33.5 (59–131)	1204 ± 293 (904–1731)	16884 ± 6624 (9124 – 24483)

Mean pharmacokinetic parameters ± sd and (range) observed for 6 subjects with twins who had sampling done daily for seven days after an injection. AUC is area under the concentration × time curve, t_{1/2} is apparent half-life, C_{max} is maximum concentration, T_{max} is time of maximum concentration, V_d is volume of distribution, F is fraction of drug bioavailable, CL represents drug clearance, C_{trough} is concentration immediately prior to subsequent dose.

TABLE 2

Population Pharmacokinetic Parameter Estimates

Parameter	Mean $\pm$ SE
Ka (day^{-1})	1.5 (Fixed)
V/F ($\times 10^3$ ltr)	62.5 ± 7.2
CL/F ($\times 10^3$ ltr/d)	1.29 ± 0.24
IIV_V	0.49 ± 0.13
IIV_CL	0.24 ± 0.04

Population pharmacokinetic parameter estimates (mean $\pm$ SE) obtained from the final model. Ka: absorption rate constant, V/F: volume of distribution/bioavailability, CL/F: apparent clearance/bioavailability, IIV: Interindividual variability in estimated pharmacokinetic parameters.