Population pharmacokinetics of high-dose tigecycline in patients with sepsis or septic shock

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Running title: Population pharmacokinetics of high-dose tigecycline

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Abstract

Background and objective: Tigecycline is a glycylcycline often used in critically ill patients as antibiotic of last resort. The pharmacokinetics (PK) of tigecycline in Intensive Care Unit (ICU) patients can be affected by severe pathophysiological changes so that standard dosing might not be adequate. The aim of this study was to describe population PK of high dose tigecycline in patients with sepsis or septic shock and evaluate relationship between individual PK parameters and patient's covariates.

Materials and Methods: The study population consisted of 37 adult ICU patients receiving 200 mg loading dose of tigecycline followed by multiple doses of 100 mg every 12 h. Blood samples were collected at 0.5, 2, 4, 8 and 12 h after dose administration. Two-compartment model with inter-individual (IIV) and inter-occasion (IOV) variability in PK parameters was used to describe the concentration-time course of tigecycline.

Results: The estimated values of mean population PK parameters were 22.1 L/h and 69.4 L/h for elimination and inter-compartmental clearance, 162 L and 87.9 L for volume of central and peripheral compartment. The IIV and IOV in clearance was lower than 20%. The estimated values of distribution volumes were different than previously published values, which might be due to pathophysiological changes in ICU patients. No systematic relationship between individual PK parameters and patient's covariates was found.

Conclusions: The developed model does not show evidence that individual tigecycline dosing adjustment based on patient's covariates is necessary to obtain the same target
concentration in patients with sepsis or septic shock. Dosing adjustments should be based on the pathogens, their susceptibility and PK targets.
1. Introduction

Tigecycline is a glycylcycline antibiotic approved by the FDA for the treatment of complicated skin and skin structure infections (cSSSI), complicated intra-abdominal infections (cIAI), and community-acquired bacterial pneumonia (CABP) (1). The pharmacokinetics of tigecycline is characterized by large volume of distribution at steady state (7 – 10 L/kg) compared to other antimicrobials and dose-independent clearance (2). The drug is eliminated mainly by fecal excretion of unchanged tigecycline with a minor renal elimination of unchanged drug, glucuronide conjugates and N-acetyl-9-aminominocycline metabolite (3). It is highly bound to plasma proteins and exhibits atypical nonlinear protein binding (4).

FDA issued a boxed warning for increased risk of death with tigecycline treatment for FDA-approved and non-approved uses, but the cause of higher mortality was not established (5). Consequently, it is advised by FDA to use tigecycline only in situations when alternative treatments are not suitable (5). Due to shortage of other effective antimicrobials and wide spectrum of tigecycline in vitro activity, including multidrug-resistant (MDR) and extensively drug-resistant (XDR) pathogens, tigecycline is often used off-label in critically ill patients as antibiotic of last resort (1, 6–8). As sepsis and septic shock are associated with high morbidity and mortality, optimization of antibiotic therapy based on informative population models might play a role in increasing patient's chance of survival (9). Standard dosing of antimicrobials results in target drug concentrations in mild-to-moderately ill patients, but in critically ill patients the pathophysiological changes may influence drug pharmacokinetics (PK) and consequently affect required dosing (10, 11).
Changes in PK of patients with sepsis or septic shock include changes in clearance caused by increased cardiac output or organ failure and shifts in volume of distribution as a result of increased vascular permeability or altered protein binding (12). Changes in physiology that alter the PK can also be caused by medical interventions such as mechanical ventilation, continuous renal replacement therapy (CRRT), extracorporeal membrane oxygenation (ECMO), etc (10, 13). As the state of the patient changes over time, dosing should be adjusted accordingly. To do so, one has to identify the relationship between measurable patient covariates and pharmacokinetic parameters.

The recommended dosage regimen for tigecycline is 100 mg initial dose, followed by 50 mg every 12 hours (1). However, dosing recommended in package insert might be insufficient in critically ill patients (14) and result in underdosing of tigecycline (15, 16). Adequate dosing of antibiotics in patients with sepsis or septic shock is of special importance as underdosing can lead to insufficient antimicrobial activity and negatively affect the patient’s outcome (10, 14). Ramirez et al (17) investigated the use of higher doses of tigecycline (150 mg followed by 75 mg every 12 h and 200 mg followed by 100 mg every 12 h) and proved them to be more effective compared to imipenem/cilastatin treatment for hospital-acquired pneumonia without adverse effects in groups with high doses of tigecycline. Similar findings were published by De Pascale et al (18), who retrospectively compared standard tigecycline dosing with 200 mg loading dose followed by 100 mg every 12 h and concluded improved outcome of patients with MDR Gram-negative ventilator-associated pneumonia in the higher tigecycline dosing group.

The objectives of this study were to describe population pharmacokinetics of high-dose tigecycline in patients with sepsis or septic shock treated in two tertiary medical/surgical...
intensive care units (ICUs) and examine the relationship between patient characteristics and individual PK parameters in order to propose dose adjustments according to patient covariate values.

### 2. Materials and Methods

#### 2.1. Patients and study design

This was a prospective, observational cohort study investigating the pharmacokinetics of tigecycline in adult patients admitted to two tertiary medical/surgical ICUs in Lublin and Olsztyn, Poland. Ethical approval was obtained from the Bioethics Committee of the Medical University of Lublin. The inclusion criteria for the study were as follows: age 18-75 years; sepsis or septic shock of both medical and surgical origin at admission to the ICUs, and suspected nosocomial infection with MDR or XDR strains, requiring the implementation of empiric broad spectrum antibiotics according to the local antimicrobial prescribing policy. Patients were excluded from the study if they had no life-threatening condition at the time of onset of symptoms of infection, were diagnosed with HIV infection or terminal cancer, displayed intolerance or allergy to tigecycline in the past, had high probability of bacterial infection with tigecycline resistant strains (e.g. Pseudomonas aeruginosa), and received tigecycline up to three months before being screened. Each patient received initial dose of 200 mg of tigecycline in a short 30 min infusion, followed by multiple doses of 100 mg in 30 min infusion every 12 h. The patients included in the study received 2 to 8 doses of tigecycline for 1 to 4 consecutive days. Arterial blood samples (2 ml) for PK analysis were collected into heparinized test tubes at 0.5, 2, 4, 8 and 12 h after each tigecycline administration. Red blood cells were
precipitated and removed by centrifugation at 10,000 rpm for 10 min. Blood plasma was collected and frozen at –80°C until used.

### 2.2. Assay

The analytical measurements of plasma samples were performed using Dionex chromatographic system (Sunnyvale, USA,) equipped with UVD340S diode array UV detector and gradient pump P580 LPG LC-6A. The samples were injected using Rheodyne 7725 loop injector with an effective volume of 20μl. The detailed chromatographic parameters of the analytical method were described in the Supplementary Material.

The analytical method was validated in terms of linearity, limit of detection and quantification, precision as well as accuracy. The method was linear over a concentration range from 0.078 to 2.5 μg/mL. The limit of detection (LOD) and limit of quantification (LOQ) were below 0.02 μg/mL and below 0.078 μg/mL, respectively. Over the range of concentrations from 0.078 to 2.5 μg/ml of tigecycline, the intra- and inter-day accuracies ranged from 98.4 to 103.1 and CVs were between 0.6 and 3.8%.

The detailed procedure of the method validation was described in the Supplementary Material.

To determine tigecycline's concentrations, plasma samples were prepared for analysis as follows: 200 μl of plasma was pipetted into a 2.5-ml plastic centrifugal filter devices (Centrifugal Filter 0.22 μm GV Durapore, Millipore Corporation, Billerica, MA, USA), to which 200μl of 0.023 M phosphate buffer solution and 400μl of acetonitrile were added and vortex-mixed for 1 min. After centrifugation (at 10,000×g for 10 min) the organic layer was removed and 20μl of the aqueous phase was injected into the HPLC system.
2.3. Pharmacokinetic modeling

Population nonlinear mixed effects modeling was conducted using NONMEM software (version 7.3, Icon Development Solutions, Ellicott City, Md, USA), GNU Fortran 95 compiler (GCC 4.6.0) and Wings for NONMEM (WFN741, http://wfn.sourceforge.net). The first-order conditional estimation method using ADVAN 3 TRANS 4 routine with η-ε interaction was employed throughout the model-building procedure. R computing environment (R Core Team 2015) was used for data processing and visualization. The first-order conditional estimation method using ADVAN 3 TRANS 4 routine with η-ε interaction was employed throughout the model-building procedure. R computing environment (R Core Team 2015) was used for data processing and visualization.

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The minimum value of the NONMEM objective function (OFV), typical goodness-of-fit diagnostic plots, and the evaluation of the precision of pharmacokinetic parameter and variability estimates were used to discriminate between various models during the model-building process. For two nested models, the difference in OFV is equal to minus twice the log likelihood and approximately $\chi^2$ distributed. A difference in OFV of 3.84 corresponds to a significance level of $P<0.05$ for one additional parameter. Goodness-of-fit plots included plots of the observed concentrations versus population and individual predicted concentrations and plots of the conditional weighted residuals (CWRES) versus individual predicted concentrations and time. A nonparametric bootstrap was performed to evaluate the uncertainty of final model parameters. The model performance was assessed by means of visual predictive check (VPC). Based on literature (17, 19, 20) and visual data inspection, a two-compartment model was used to describe plasma tigecycline concentration-time profile. The model was parametrized in terms of clearances ($CL$ and $Q$ denoting metabolic inter-compartmental clearances, respectively) and volumes of distribution ($V_1$ and $V_2$ denoting the volumes of distribution...
of central and peripheral compartment, respectively). The sum of \( V_1 \) and \( V_2 \) is the volume of distribution at steady state (\( V_{ss} \)).

Inter-individual variability (IIV) and inter-occasion variability (IOV) of the PK parameters were modeled in terms of \( \eta \) and \( \kappa \) variables, respectively. The \( \eta \) variables were used to model differences between the individuals and \( \kappa \) variables were used to model differences between occasions within the individuals. The \( \eta \) and \( \kappa \) variables were assumed to have log-normal distributions with mean 0 and variances \( \omega^2 \) and \( \pi^2 \), respectively. The IIV and IOV variances were assumed to be constant across occasions. The individual value of a PK parameter on a certain occasion was defined as:

\[
P_{ik} = \theta_P \exp(\eta_{P,i}) \exp(\kappa_{P,i,k})
\]

where \( P_{ik} \) is the individual PK parameter on a certain occasion, \( \theta_P \) is the typical value of this PK parameter in the population, \( \eta_{P,i} \) is a random effect for that PK parameter associated with between-individual variability and \( \kappa_{P,i,k} \) is a random effect for the individual parameter associated with within-individual variability.

The residual error for observations was modeled using combined additional and proportional error model with \( \epsilon_{prop,ik} \) and \( \epsilon_{add,ik} \) representing the proportional and additive components of residual variability of tigecycline concentrations. It was assumed that \( \epsilon_{prop} \) and \( \epsilon_{add} \) variables have normal distribution with the mean 0 and variances \( \sigma^2_{prop} \) and \( \sigma^2_{add} \), respectively.
The covariates considered for testing included time-independent covariates: age, weight, height, sex, application of extracorporeal techniques (ECMO and CRRT), as well as the time-dependent covariates: dialysis volume, ultrafiltration (UF) speed, extravascular lung water index (ELWI), cardiac output (CO), sequential organ failure assessment (SOFA) score and procalcitonin (PCT) concentration. To identify possible relationships, covariate search was performed by plotting random effects of parameters against covariates. For the model including IIV, the estimates of the η values were plotted against time-independent covariates and the median values of time-dependent covariates. For the model including both IIV and IOV, the estimates of the κ values were plotted against time-dependent covariates. As no apparent visual relationship was found, formal statistical testing was not employed.

3. Results

The analyzed data consisted of 942 observations of tigecycline concentration obtained from 37 patients. Patients characteristics are summarized in Table 1. Two measurements were identified as outliers during model building process (CWRES>5) and excluded from the analysis. A summary of the patients characteristics is presented in Table 1. The change in time-dependent covariates in the population during 3 subsequent days of therapy are shown in supplementary Figure S1.

The raw concentration data is shown in Figure 1. A two-compartment disposition model was used to describe the available data. Inter-individual variability was estimated for CL, V1 and V2, but it was not possible to estimate the IIV for Q2. Visual covariate search was performed for this model, but no systematic relationship was found.
As for each patient data were available on multiple dosing occasions, inter-occasion variability in individual PK parameters was investigated. In the final population model IOV was estimated for individual $CL$ and $V2$ parameter values.

Table 2 shows parameter estimates of the final population PK model of tigecycline along with their bootstrap estimates. All PK parameters, inter-subject, inter-occasion and residual error variances were estimated well with $RSE$ lower than 66%. The estimates of the model parameters fell very close to the median estimates obtained from bootstrap, which proves the final model estimates to be unbiased.

Goodness-of-fit plots of the final model are presented in supplementary Figure S2. The individual and population predictions versus observed concentrations are relatively symmetrically distributed around the line of identity. The conditional weighted residuals versus time and versus individual predicted concentrations do not show any trend and are relatively evenly distributed around zero. The VPC plot presented in Figure 2 indicates that both the central tendency of the data and the variability at a particular sampling time were recaptured very well. The individual predicted concentration versus time profiles were very close to the experimental data as presented in supplementary Figure S3.

In the final model the typical values of elimination and inter-compartmental clearance were 22.1 L/h and 69.4 L/h. The typical values of volume of central and peripheral compartment were 162 L and 87.9 L. The inter-individual variability was intermediate for $CL$ (17.3%) and $V1$ (19.2%) and higher for $V2$ (38.7%). The inter-occasion variability for $CL$ and $VT$ was 14.4% and 20.8%. The shrinkage for $\eta$ was low (7.3% for $CL$, 6.7% for
124 \( V1, 22\% \text{ for } V2 \), while for \( \kappa \) it was generally higher, reaching >90\% for occasion 7 and 8, where only few observations were available.

126 The relationships between the individual values of \( CL \) and \( Vss \) and time-independent covariates are presented in Figure 3. The relationships between the estimates of \( \kappa \) for the individual \( CL \) and \( V2 \) values and the time-dependent covariates are presented in Figure 4. The relationships between the estimates of \( \eta \) for \( CL \), \( V1 \) and \( V2 \) versus individual values of the time-independent covariates and median values across occasions of time-dependent covariates are presented in supplementary Figures S4-S6.

127 The lack of any regular trend in the data indicates that the analyzed covariates cannot explain the remaining unexplained between-patient and between-occasion variability. The relationship between the individual values of \( CL \) and variables calculated based on weight and height i.e. BSA and BMI was additionally explored, but no trend was discovered.

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4. Discussion

129 The comparison of the mean PK parameter values obtained in this study with selected literature values (17, 19, 20) is presented in Figure 5. The estimated mean value of clearance is consistent with the published studies (17, 19–21), it is also in good agreement with tigecycline product information \((CL=24 \text{ L/h})\) (1). A study by Xie et al (22) in critically ill patients reports lower clearance of 7.5 L/h; however, this value was estimated based on small population (10 patients). Overall, the expected AUC and average concentration achieved after tigecycline administration is consistent across the studies. Good estimation of clearance is the most important for
safety and efficacy of therapy, especially in the context of boxed warning issued
tigecycline by FDA (5). In our study the clearance IIV (17.3%) was estimated to be
approximately two times smaller than in other studies (17, 19, 20), but part of the
variability in clearance (14.4%) of assigned to IOV. This suggests that the variability in
tigecycline clearance is caused by differences between the patients as well as the
differences within the patient on various occasions. Small inter-individual and inter-
occasion variability in clearance suggests that to obtain the same target concentration in
all patients, uniform dosing of tigecycline is sufficient in critically ill patients. To find
clinically significant relationship between covariate and parameter, the relationship
should lead to reduction in the variability of this parameter by 20%. In our case, with IIV
and IOV lower than 20%, it is not possible.

The values of intercompartmental clearance are similar between the studies as shown
in Figure 5, but estimated with different precision. Lower precision of $Q$ value estimate
in our study is due to little information about this parameter from the applied sampling
design.

The values of volumes of distribution differ between the studies. Mean $V_{ss}$ in our study
is 250 L, which is comparable to the value of 298 L estimated by Ramirez et al (17), but
very different from the studies by Rubino et al (20) and Van Wart et al (19), which can
be observed in Figure 5. Additionally, the study in healthy subjects reports $V_{ss}$ between
490 and 700 L in a 70-kg patient (21). Precise estimates of the volume of peripheral
compartment require very long sampling schedules, since they are based on the
terminal part of concentration-time profile. In our study, the sampling after the last dose
is rather short, which might cause imprecise and biased $V_2$ estimates. Even though $V_2$
value in the study by Van Wart et al (19) is very high, the precision of this estimate is poor. The differences in the values of distribution volumes of central and peripheral compartment can be observed in Figure 6, where simulation of tigecycline concentrations based on parameters from 3 studies with dosing applied in our study is presented. The value of V1 in our study is approximately 1.5-fold higher than in study by Van Wart et al (19) and 2.5-fold higher than in study by Rubino et al (20). This determines lower predicted peak concentrations after dose administration in our study and lower peak-trough fluctuation after multiple administration. The value of volume of peripheral compartment in our study is several fold lower than the literature values (19, 20), which results in lower drug accumulation after multiple administration (accumulation ratio 1.57 in our study compared to 4.00 (19) and 2.55 (20)). The shift between the distribution volumes in our study might possibly occur due to changes in physiology caused by the sepsis/septic shock of the patients in the analyzed population. Increased capillary permeability in sepsis causes the shift of the fluids from blood vessels to interstitial space, which can increase the volume of distribution of the central compartment (9). The hypoalbuminemia present in critically ill patients can also affect the volume of distribution, especially since tigecycline is highly bound to proteins and shows nonlinear plasma protein binding (16). This is not supported by the study in critically ill patients by Xie et al (22), where the estimated value of V1 was approximately half of the value estimated in our study (72.5 L and 162 L, respectively). Tigecycline is a lipophilic antibiotic and as such, its volume of distribution at steady state should not be altered due to physiological changes of the patients in the ICU (12).
None of the covariates showed a clear relationship with the individual values of PK parameters, which is consistent with the results of Ramirez et al (17), but not with two other studies, which included the relationship of $CL$ versus body surface area and creatinine clearance (20) and $CL$ versus weight, creatinine clearance and gender (19) in the final model. In the study by Xie et al (22) BMI was included in the model as a linear predictor of $CL$, but this inclusion was not supported by improvement in log likelihood value. On the other hand, no relationship between $CL$ and body weight was reported in a study in obese patients by Pai (23). Honore et al (24) suggested influence of CRRT on tigecycline PK; however, the group of patients who did not receive CRRT in this study was too small to assess the impact of CRRT on individual PK parameters.

Individualized dosing of antimicrobials based on patient's characteristics is important for safety and efficacy of the therapy, but the main issue for the clinician is to determine and obtain PK target for the pathogen, which is based on the minimal inhibitory concentration (MIC) (14). Since our study suggests that there is no strong relationship between tested patient's covariates and individual PK parameters for tigecycline in critically ill patients, dosing adjustments should be focused on identification of pathogens, their susceptibility and determination of PK target. With identified target plasma concentration, the dose of tigecycline can be calculated based on estimated PK parameters from our model.

### 5. Conclusions

The population PK model was successfully developed to describe the time course of tigecycline concentrations in patients with sepsis or septic shock. None of the available
patient's covariates was identified to explain part of the IIV or IOV in the pharmacokinetic parameters, therefore no individual dosing adjustment could be proposed based on the available patient's covariates. Low inter-individual and inter-occasion variability in clearance suggests that assuming the same target concentration in all patients, uniform dosing in this population is sufficient and dosing adjustments should be based on the pathogens, their susceptibility and PK targets. The model can be useful for further analysis of tigecycline exposure-response relationships in critically ill patients.

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**Figure legends**

Fig. 1 Individual tigecycline concentration-time profiles of the studied population

Fig. 2 The Visual Predictive Check showing the simulation-based 90% confidence intervals around the 5th, 50th, and 95th percentiles of the PK data in the form of turquoise (50th) and violet (5th and 95th) areas; the corresponding percentiles from the observed data are plotted in black color

Fig. 3 The estimates of individual PK parameters from the final model in relation to time-independent continuous covariates and categorical covariates; the grey lines indicate the trend in the data (loess smooth); CL – clearance, Vss – volume of distribution at steady state, ECMO – extracorporeal membrane oxygenation, CRRT – continuous renal replacement therapy, SDT – started during therapy

Fig. 4 The individual estimates for kappa of the final PK parameters in relation to time-dependent covariates; the grey lines indicate the trend in the data (loess smooth); κ – deviation of individual parameters between occasions, CL – clearance, V2 – volume of distribution of the peripheral compartment, ELWI – extravascular lung water index, CO – cardiac output, SOFA – sequential organ failure assessment score, PCT – procalcitonin concentration

Fig. 5 The comparison of the population PK parameter values estimated in our study and the studies of Van Wart et al [15], Rubino et al [16] and Ramirez et al [13]; the boxplots show the mean value and standard deviation of the parameter; for the study by Rubino et al [16] the standard deviation of the mean clearance estimate was obtained from bootstrap results; CL – clearance, Vss – volume of distribution at steady state, Q – intercompartmental clearance, V1 – volume of distribution of the central compartment,
Fig. 6 The simulation of tigecycline concentrations after 200 mg loading dose and seven 100 mg subsequent doses in 12 h intervals based on typical population PK parameters from the model developed in this study (black solid lines) and the models published by Van Wart et al [15], Rubino et al [16] and Ramirez et al [13] (red dashed lines).
Table 1. Demographic and medical condition characteristics of the patients in the study population; values are expressed as median and range for continues and as count for categorical variables; ECMO – extracorporeal membrane oxygenation, CRRT – continuous renal replacement therapy, ELWI – extravascular lung water index, SOFA – sequential organ failure assessment score

| Parameter [unit]                      | Median [Range] n=37 |
|--------------------------------------|---------------------|
| Age [years]                          | 61 [25 - 79]        |
| Weight [kg]                          | 80 [50 - 129]       |
| Height [cm]                          | 175 [158 - 190]     |
| Male/Female                          | 26/11               |
| Death/Survival                       | 23/14               |
| ECMO No/Yes                          | 35/2                |
| CRRT No/Yes/Started during therapy   | 6/30/1              |
| Dialysis [mL/kg]                     | 23.8 [14.2 - 40.0]  |
| Ultrafiltration [mL/kg/h]            | 1.54 [0.34 - 6.6]   |
| ELWI [mL/kg]                         | 9 [5 - 41]          |
| Cardiac output [L]                   | 7.49 [2.55 - 15.8]  |
| SOFA score                           | 13 [2.0 - 21]       |
| Procalcitonin concentration [µmol/L]| 8.22 [0.16 - 122]   |
| Albumin concentration [g/dl]         | 2.2 [1.5-3.6]       |
Table 2. Final model parameter estimates. 90% confidence interval (CI) of the parameter estimate derived from a nonparametric bootstrap analysis (n=1000, unsuccessful=1); $\sigma_{add}$ – additive residual random error, $\sigma_{prop}^2$ – variance of proportional residual random error, RSE – relative standard error, CV – coefficient of variation, CL – clearance, Vss – volume of distribution at steady state, Q – intercompartmental clearance, V1 – volume of distribution of the central compartment, V2 – volume of distribution of the peripheral compartment

| Parameter | Estimate | RSE (%) | shrinkage (%) | Bootstrap median | Bootstrap 90% CI |
|-----------|----------|---------|---------------|-----------------|-----------------|
| Mean population parameters ($\theta$) |
| $\theta_{CL}$ [L/h] | 22.1 | 3.16 | 22.1 | 20.9 - 23.2 |
| $\theta_{V1}$ [L] | 162 | 5.3 | 163 | 150 - 176 |
| $\theta_{Q}$ [L/h] | 69.4 | 32.6 | 67.3 | 41.9 - 98.4 |
| $\theta_{V2}$ [L] | 87.9 | 8.67 | 87.6 | 76.1 - 101 |
| Inter-individual variability ($\omega^2$) |
| $\omega^2_{CL}$ (%CV) | 17.3 | 19 | 7.3 | 17.1 | 14.2 - 19.7 |
| $\omega^2_{V1}$ (%CV) | 19.2 | 29.2 | 6.7 | 19.1 | 14.3 - 23.7 |
| $\omega^2_{Q}$ (%CV) | 0 FIX | – | – | – | – |
| $\omega^2_{V2}$ (%CV) | 38.7 | 40.8 | 22.4 | 37.4 | 20.4 - 48.5 |
| Inter-occasion variability ($\pi^2$) |
| $\pi^2_{CL}$ (%CV) | 14.4 | 35 | 14.2 | 9.4 - 18.1 |
| Occasion 1 | | | | 27.4 |
| Occasion | Value |
|----------|-------|
| 1        | 40.2  |
| 2        | 50.2  |
| 3        | 58.5  |
| 4        | 56.4  |
| 5        | 52.9  |
| 6        | 57.2  |
| 7        | 90.6  |
| 8        | 99.6  |

Residual error model

| Parameter | Value |
|-----------|-------|
| $\sigma_{\text{add}}$ (µg/ml) | 0.0210 |
| $\sigma_{\text{prop}}^2$ (%CV) | 13.0   |

\begin{align*}
\pi^2_{\text{CV}} &= 20.8, \quad 66.4, \quad 21.7, \quad 0.200 - 30.9 \\
\sigma_{\text{add}}^2 &= 0.0210, \quad 0.41, \quad 0.0224, \quad 0.000209 - 0.0357 \\
\sigma_{\text{prop}}^2 &= 13.0, \quad 17.7, \quad 12.7, \quad 8.89 - 16.1
\end{align*}
