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# A Population Pharmacokinetic Analysis of Voriconazole and Development of a Personalized CYP2C19 Genotype-Guided Voriconazole Dosing Regimen

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서울대학교 대학원
의과학과 의과학전공

김 윤

A thesis of the degree of Doctor of Philosophy

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August 2019

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# A Population Pharmacokinetic Analysis of Voriconazole and Development of a Personalized CYP2C19 Genotype–Guided Voriconazole Dosing Regimen

by
Yun Kim

A thesis submitted to the Department of Biomedical Sciences in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Medicine at Seoul National University College of Medicine

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# ABSTRACT

## A Population Pharmacokinetic Analysis of Voriconazole and Development of a Personalized CYP2C19 Genotype-Guided Voriconazole Dosing Regimen

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**Introduction:** Voriconazole is a broad-spectrum antifungal agent for the treatment of invasive aspergillosis. Highly variable and non-linear pharmacokinetics of voriconazole is known to be caused by many factors including CYP2C19 genotype, demographics, drug-drug interactions, and liver function. Above all, CYP2C19 genotype is an important intrinsic determinant of voriconazole exposure. However, the comprehensive effect of CYP2C19 genotype on voriconazole pharmacokinetics was not quantitatively identified. This study aimed to develop a mechanistic population pharmacokinetic model of voriconazole including the CYP2C19 genotype, and to assess the appropriateness of various dosing regimens based on the

therapeutic target.

Methods: This study included pharmacokinetic data obtained from healthy volunteers and patient populations who participated in five clinical studies with voriconazole. Subjects received single and multiple intravenous and/or oral dosing of voriconazole. A total of 1,828 concentrations from 193 subjects were included in the population pharmacokinetic analysis. The effects of demographics, CYP2C19 genotypes, liver function related parameters, and co-medication on the pharmacokinetics of voriconazole were evaluated. A model-based simulation was performed using NONMEM to evaluate the probability of attainment of the therapeutic target.

Results: A three-compartment model with an inhibition compartment appropriately described the voriconazole pharmacokinetics reflecting auto-inhibitory characteristic of voriconazole. Voriconazole clearance in the CYP2C19 intermediate metabolizers (IMs) and poor metabolizers (PMs) decreased by 17% and 53% compared to that in the extensive metabolizers (EMs). There was a time-dependent inhibition of clearance to 16.2% of its original value in the CYP2C19 EMs, and the extent of inhibition differed according to the CYP2C19

genotypes. Approximately 47% reduction in clearance was observed in patients with impaired liver function. The proposed CYP2C19 genotype-guided initial dosing regimens are 400 mg twice daily (bid) for EMs, 200 mg bid for IMs, and 100 mg bid for PMs.

**Conclusion:** This study was the first attempt to mechanistically explain the non-linear pharmacokinetics of voriconazole using an inhibition compartment model with incorporation of CYP2C19 phenotype effect. The CYP2C19 genotype-guided initial dosing regimen based on the final model will provide a rationale to individualize optimal dosing to improve clinical outcomes with voriconazole therapy.

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**Keywords:** Antifungal agent; Population Pharmacokinetics; Pharmacogenetics; infectious disease; Individualized Pharmacotherapy

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| | |
|---|---|
| ALAG | Absorption lag time |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| AUC | The area under the concentration-time curve |
| BMI | Body mass index |
| BW | Body weight |
| CI | Confidence interval |
| $C_{inh}$ | Concentration in the inhibition compartment |
| $C_{max}$ | Maximum plasma concentration |
| CL | Clearance |
| CV | Coefficient of variation |
| CWRES | Conditional weighted residual |
| CYP | Cytochrome P450 |
| DDI | Drug-drug interaction |
| F | Bioavailability |
| GOF | Goodness-of-fit |
| h | hour(s) |

| | |
|---|---|
| $IC_{50}$ | Concentration in the inhibition compartment yielding 50% of maximum clearance inhibition |
| IIV | Inter-individual variability |
| INH | Inhibition fraction of clearance |
| IV | Intravenous |
| $K_a$ | Absorption rate constant |
| $K_{IC}$ | Rate constant into inhibition compartment |
| LF | Liver function |
| OFV | Objective function value |
| pcVPC | Prediction-corrected visual predictive check |
| $Q_2$, $Q_3$ | Inter-compartmental clearance |
| PK | Pharmacokinetics |
| RCLF | Remaining clearance fraction |
| RSE | Relative standard error |
| SD | Standard deviation |
| TDM | Therapeutic drug monitoring |
| $V_2$ | Central volume of distribution |
| $V_3$, $V_4$ | Peripheral volume of distribution |

# INTRODUCTION

Voriconazole is the first available second-generation antifungal agent used for the treatment of various fungal infections [1, 2]. Voriconazole shows extended spectrum of antifungal activity against clinically significant pathogens, including *Aspergillus, Candida, Cryptococcus neoformans*, as a synthetic derivative of fluconazole, which could overcome possible resistance and become the drug of choice for long-term treatment [2]. The mechanism of action of voriconazole is to prevent biosynthesis of ergosterol from lanosterol by inhibiting fungal cytochrome P450 (CYP)-dependent 14α-sterol demethylase, which is an essential step in the synthesis of the cell membrane [1]. Voriconazole has been widely used in clinical settings and administered either intravenously or orally because of its excellent bioavailability (approximately over 90%) [3]. However, the clinical use of voriconazole is limited due to adverse events such as visual disturbances, hepatotoxicity, and central nervous system dysfunctions, which are related to high exposure of voriconazole. For this reason, voriconazole requires therapeutic drug monitoring (TDM) in clinical practice [4-6].

Voriconazole exhibits highly variable and non-linear

pharmacokinetics, which shows a supra-proportional increase in its exposure with increasing dose administered. This is contributed by many factors, including age, liver function, CYP2C19 phenotype, saturation and auto-inhibition of its own metabolism, and drug-drug interactions (DDIs) [3, 7-9]. It has been demonstrated that after a single intravenous or oral dose, voriconazole exposure in the CYP2C19 poor metabolizers (PMs) was more than three times that of the extensive metabolizers (EMs) [9]. This supports the fact that the CYP2C19 phenotype is a critical factor responsible for the variability of voriconazole pharmacokinetics. Voriconazole undergoes hepatic metabolism predominantly by CYP2C19 and also by CYP2C9 and CYP3A4 to a lesser extent to form N-oxide as its major metabolite [3]. In vitro studies have shown that the N-oxide metabolite of voriconazole inhibits its own metabolism [10]. It was also recently confirmed in humans that both voriconazole and its N-oxide metabolite inhibit CYP3A4 and also CYP2C19 to a lesser extent even stronger at the steady-state concentration [11, 12]. The inhibition mechanism of CYP3A4 by voriconazole has been described with dynamic changes of CYP3A activity at liver and gut wall (major expression sites) [13]. The extent of this auto-

inhibition can vary according to the CYP2C19 genotypes. Therefore, all these contributing factors constantly add to the difficulty of maintaining voriconazole concentration within the therapeutic range (2.0–5.5 mg/L) [14, 15].

Owing to the large inter- and intra-subject variability of voriconazole pharmacokinetics, TDM is recommended by the United States Food and Drug Administration and the Infectious Diseases Society of America [14, 16]. Various intrinsic and extrinsic factors may result in unpredictable pharmacokinetics of voriconazole [14]. With proper use of TDM, voriconazole therapy can lead to fewer treatment discontinuations owing to its diverse adverse reactions, including visual disturbances, elevated liver function tests, dermatological reactions, and hallucinations. The proportion of treatment discontinuation due to adverse reactions was significantly lower in the patients with TDM performed (TDM vs. no TDM: 4% vs. 17%) [17]. In addition to safety, TDM can also improve the efficacy of voriconazole therapy as observed by the number of complete or partial responses (TDM vs. no TDM: 81% vs. 57%) in invasive fungal infections [17]. The current clinical use of TDM for voriconazole is to allow dose adjustments after the first few days of initiation of the standard

dosing regimen. However, unexpected adverse reactions and deviations from the therapeutic range can occur at the beginning of the treatment before performing TDM.

Accordingly, the need for development of an initial dosing regimen for voriconazole has been growing. The initial dose selection based on the CYP2C19 genotype can detect patients at high risk of exposure before the drug administration itself, and can ultimately help to reach optimal therapeutic concentration timely and accurately. The CYP2C19 genotype-guided dosing regimen is supported by some recent studies, which represent that genotype-directed dosing can help pediatric and renal transplanted patients to timely achieve the therapeutic target concentration [18, 19]. However, the current Clinical Pharmacogenetics Implementation Consortium (CPIC®) guideline for voriconazole therapy still lacks adequate information on the initial dosing based on the CYP2C19 genotype [20]. Therefore, this study was performed to develop a population pharmacokinetic model of voriconazole that reflected the influence of intrinsic factors such as the CYP2C19 genotype, and to assess the appropriateness of various dosing regimens according to the CYP2C19 phenotypes.

# METHODS

## Study Population

This study included pharmacokinetic data obtained from healthy volunteers and patient populations who participated in five different clinical studies with voriconazole conducted at the Seoul National University Hospital (Table 1) [9, 17, 21, 22]. All subjects gave their informed consent for inclusion before they participated in the clinical studies. The clinical studies were conducted in accordance with the Declaration of Helsinki, and the protocols were approved by the institutional review board of Seoul National University Hospital (Seoul, Republic of Korea; Table 1; H-0811-004-261, H-1207-057-417, H-1607-160-779, H-0808-057-254).

The study population in each clinical study (study 1-4: healthy volunteers, and study 5: patients) received intravenous or oral voriconazole with predefined study designs, as follows:

- Study 1: a single dose of intravenous voriconazole 200 mg, followed by single and multiple doses of oral voriconazole 200 mg every 12 h [9],
- Study 2: a single dose of oral voriconazole 400 mg [22],

- Study 3: a single dose of intravenous voriconazole 200 mg [21],
- Study 4: a single dose of intravenous voriconazole 200 mg, followed by a single dose of oral voriconazole 200 mg (Sang Won Lee. Oral absorption of voriconazole is affected by SLCO2B1 c.*396T>C genetic polymorphism in CYP2C19 poor metabolizers. unpublished data, 2019),
- Study 5: loading dose of intravenous voriconazole 6 mg/kg or oral voriconazole 400 mg every 12 h on the first day, followed by TDM-based maintenance doses of intravenous voriconazole 4 mg/kg or oral voriconazole 200 mg every 12 h [17].

The CYP2C19 phenotypes were classified as EMs, intermediate metabolizers (IMs), and PMs based on the CPIC® guideline, as follows: EM, *1/*1; IM, *1/*2, *1/*3, *2/*17; PM, *2/*2, *2/*3, and *3/*3 [20]. One patient identified as a rapid metabolizer (*1/*17) was considered EM for analysis.

**Table 1.** Detailed information on the pharmacokinetic data of each clinical study.

| | Clinical studies | | | | |
|---|---|---|---|---|---|
| | **Study 1** [9] | **Study 2** [22] | **Study 3** [21] | **Study 4 (unpublished data)** | **Study 5** [17] |
| Population | Healthy subjects | Healthy subjects | Healthy subjects | Healthy subjects | Patients |
| Number of subjects | 18 | 12 | 51 | 12 | 100 |
| Treatments | Single 200 mg IV (day 1) and single 200 mg PO (day 8) followed by multiple 200 mg PO bid (day 9–14) | Single 400 mg PO | Single 200 mg IV | Single 200 mg IV (day 1) and single 200 mg PO (day 8) | Loading doses of 6 mg/kg IV or 400 mg PO bid (day 1), followed by TDM based maintenance dose |
| PK sampling time | • **Single IV on day 1**<br>– Pre–dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 h post–dose<br>• **Single PO on day 8**<br>– Pre–dose, 0.5, 1, | • **Single PO on day 1**<br>– Pre–dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 h post–dose | • **Single IV on day 1**<br>– Pre–dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 h post–dose | • **Single IV on day 1**<br>– Pre–dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72 h post–dose<br>• **Single PO on day 8** | • **IV or PO after day 4**<br>– Trough levels 4 days after treatment initiation<br>• **Total 249 points** |

| | | | | | |
|---|---|---|---|---|---|
| | 1.5, 2, 3, 4, 6, 8, 12, 24 h post-dose<br>• Multiple PO on day 9-14<br>- trough levels on day 12 and 13; and pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 h post-dose on day 14<br>• Total 587 points | • Total 117 points | • Total 593 points | - Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72 h post-dose<br>• Total 282 points | |
| IRB number | H-0811-004-261 | | H-1207-057-417 | H-1607-160-779 | H-0808-057-254 |
| NCT number | NCT00942773 | NCT01080651 | NCT01657201 | NCT02906176 | NCT00890708 |

IV, intravenous; PO, oral; bid, twice daily; TDM, therapeutic drug monitoring

## Population Pharmacokinetic Analysis

A population pharmacokinetic analysis from logarithmically-transformed concentration data was performed using a non-linear mixed effects modeling approach with NONMEM (version 7.3.0, Icon Development Solutions, Ellicott City, MD, USA). The first-order conditional estimation method with the interaction option was employed to estimate the pharmacokinetic parameters and their variabilities. The population pharmacokinetic model of voriconazole was constructed using the healthy volunteers' data at first, which is an intensively sampled pharmacokinetic data and sequentially developed by incorporating sparsely sampled patients' data for further development of the model.

The structure model was selected by exploring one-, two-, and three-compartment models with a linear and/or non-linear elimination (i.e., Michaelis-Menten) model. In addition, a hypothetical inhibition compartment was included in the model and evaluated whether it helps adequately describe the non-linear time-dependent pharmacokinetics [23]. This was an exploration considering the clearance (CL) dependent on the concentration in an inhibition compartment, which is a similar

approach of incorporating an effect compartment. The absorption profile of oral voriconazole was described by a first-order process with a lag time, and the absolute bioavailability (F) was estimated using a logit model based on the available pharmacokinetic data. The inter-individual variability for each pharmacokinetic parameter was evaluated using an exponential error model. To describe the residual unexplained variability, three types of residual error models, including additive, proportional, and combined additive and proportional residual error models were tested for the healthy volunteers' and the patients' data independently.

The effect of the potential covariates on the pharmacokinetics of voriconazole was investigated graphically and statistically using a stepwise forward selection and backward elimination approach. The continuous covariates examined were as follows: age, body weight, body mass index, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatinine, and estimated glomerular filtration rate. These covariates were tested in the model using power functions normalized to their median values or generally accepted typical value (e.g., 70 kg for body weight). The categorical covariates,

including sex, CYP2C19 phenotype, liver function abnormality grade according to the Common Terminology Criteria for Adverse Events (version 4.0) [24], and co-medications such as proton pump inhibitors (PPIs such as omeprazole, pantoprazole, and lansoprazole) or glucocorticoids were investigated using exponential functions. The CYP2C19 phenotype effects were tested using separate categories of IM and PM referenced to EM. A covariate was considered to be statistically significant and finally retained in the model when the objective function value (OFV) decreased > 3.84 ($p < 0.05$, $\chi^2$ distribution with 1 degree of freedom) during forward selection, and increased > 6.63 ($p < 0.01$, $\chi^2$ distribution with 1 degree of freedom) during backward elimination. Only the biologically plausible parameter–covariate relationships were considered and included in the final model.

## Model Selection and Validation

Throughout the model development process, model selection was evaluated based on the goodness of fit plots, the estimates, precision of parameters, and the decrease in OFV. The goodness of fit plots consisted of four plots as follows: observations versus population predictions, observations versus individual

predictions, conditional weighted residuals versus population predictions, and conditional weighted residuals versus time. The predictive performance of the model for healthy volunteers' data was assessed graphically by prediction-corrected visual predictive checks (pcVPCs) performed by stratification of the CYP2C19 phenotype (EM, IM, and PM), route of drug administration (intravenous or oral), and dosing frequency (single or multiple administration). The adequacy of the model was demonstrated by plotting the time course of the observations along with the prediction interval for the simulated values. The predictive performance of the model for the patients' data was assessed in terms of bias and precision by calculating the numerical estimates of the mean prediction error (MPE in percentage; equation 1) and the relative root mean squared error (RMSE in percentage; equation 2), respectively [25]. In addition, we performed simulation-based graphical diagnostics for the patients' data by plotting normalized prediction distribution errors (NPDE) versus time and population predictions to detect any types of model misspecification [26].

$$\mathrm{MPE} = \frac{1}{n}\sum_{i=1}^{n}\left(\frac{C_{pred} - C_{obs}}{C_{obs}}\right), \quad (1)$$

$$RMSE = \sqrt{\frac{1}{n}\sum_{i=1}^{n}\left(\frac{C_{pred} - C_{obs}}{C_{obs}}\right)^2} \quad (2)$$

## Model-Based Simulation

Based on the final parameter estimates of the developed model, model-based simulations were performed to predict the concentration profiles of voriconazole according to the CYP2C19 phenotypes after multiple oral doses of different dosing regimens. The simulated dosing regimens included the standard oral dose (400 mg every 12 h on the first day followed by 200 mg every 12 h) and various test doses according to the CYP2C19 phenotypes (400 mg every 12 h on the first day followed by 100–400 mg every 12 h). The simulation was done for 7 days, which is considered sufficient to achieve the theoretical steady-state. Using the simulated voriconazole concentration according to the CYP2C19 phenotypes, the probability of attainment of the therapeutic target was calculated, where the target voriconazole trough concentration was predefined as the currently used therapeutic range of 2.0–5.5 mg/L [14, 15].

# RESULTS

## Demographics

A total of 1,828 voriconazole plasma concentration–time data from 93 healthy volunteers (1,579 observations) and 100 patients (249 observations) were included in the population pharmacokinetic analysis (Table 2). Of the total 193 studied population, 164 (85%) were males. The age of the study population ranged from 18 to 80 years, and the body weight ranged from 40.8 to 88.5 kg. The proportions of the CYP2C19 phenotype in EM, IM, and PM were 39% (n = 75), 36% (n = 70), and 25% (n = 48) respectively.

Table 2. Demographic and clinical characteristics of study population.

| Variables | Total (n = 193) | Healthy Subjects [a] (n = 93) | Patients [b] (n = 100) |
|---|---|---|---|
| Age (years) | 34 (18–80) | 26 (20–41) | 59 (18–80) |
| Weight (kg) | 66.0 (40.8–88.5) | 70.3 (57.6–88.5) | 59.4 (40.8–86.4) |
| Aspartate aminotransferase (U/L) | 21 (7–377) | 18 (9–40) | 30 (7–377) |
| Alanine aminotransferase (U/L) | 21 (4–363) | 15 (4–52) | 29 (4–363) |
| Sex | | | |
| Male | 164 (85) | 93 (100) | 71 (71) |
| Female | 29 (15) | – | 29 (29) |
| CYP2C19 phenotype | | | |
| Extensive metabolizer | 75 (39) | 32 (34) | 43 (43) |
| Intermediate metabolizer | 70 (36) | 27 (29) | 43 (43) |
| Poor metabolizer | 48 (25) | 34 (37) | 14 (14) |
| Liver function abnormality [c] | | | |
| Grade 0 | 165 (85.5) | 93 (100) | 72 (72) |
| Grade 1 | 9 (4.7) | – | 9 (9) |
| Grade 2 | 13 (6.7) | – | 13 (13) |
| Grade 3 | 5 (2.6) | – | 5 (5) |

| | | | |
|---|---|---|---|
| Grade 4 | 1 (0.5) | – | 1 (1) |
| Co-medication | | | |
| Proton pump inhibitors | 22 (11.4) | – | 22 (22) |
| Steroids | 9 (4.7) | – | 9 (9) |

Data were presented as number of subjects (%) except for age, weight, aspartate aminotransferase, and alanine aminotransferase which were presented as median (range). [a] Study 1-4; [b] Study 5; [c] Liver function abnormality according to Common Terminology Criteria for Adverse Events (version 4.0).

## Population Pharmacokinetic Model

A three-compartment model with a first-order oral absorption, an absorption lag time, and elimination along with an inhibition compartment model appropriately described the time-concentration profile of voriconazole, showing distinct non-linear pharmacokinetic behavior (Figure 1). The inhibition compartment reflected the auto-inhibition of voriconazole metabolism, as well as a time-dependent CL profile by multiplying the inhibition fraction of voriconazole CL (INH) to the initial CL ($CL_0$). The equations for the CL and INH are as follows:

$$CL = CL_0 \times INH, \quad (3)$$

$$INH = RCLF + (1 - RCLF) \cdot \left(1 - \frac{C_{Inh}}{IC_{50} + C_{Inh}}\right) \quad (4)$$

That is, the voriconazole CL is inhibited depending on the concentration in the empirical inhibition compartment over time. In this inhibition time course, CL is able to take values ranging from 0 to 100% of the initial value, which is determined by the time of the first administration of voriconazole. The remaining CL fraction (RCLF), as an estimable parameter in the model, represents the fraction of the voriconazole CL that cannot be inhibited at the steady state. If RCLF is close to 0, then it

corresponds to approximately 100% CL inhibition, while if RCLF is close to 1, then it corresponds to almost no CL inhibition. In addition, $C_{Inh}$ is the concentration in the inhibition compartment, and $IC_{50}$ is the $C_{Inh}$ yielding 50% of maximum CL inhibition. Additionally, a rate constant was added to the inhibition compartment ($K_{IC}$) to explain the time course of CL inhibition.

The absorption rate constant of 1.23 $h^{-1}$ and the lag time of 0.237 h appropriately described the absorption phase of orally administered voriconazole. The absolute oral bioavailability of voriconazole was estimated to be 87.6%. The estimated typical CL of voriconazole was 45.3 L/h, which was expected to be inhibited over time up to 16.2% of its original value (7.3 L/h). Most of the typical parameter values were estimated with a good precision (Table 3).

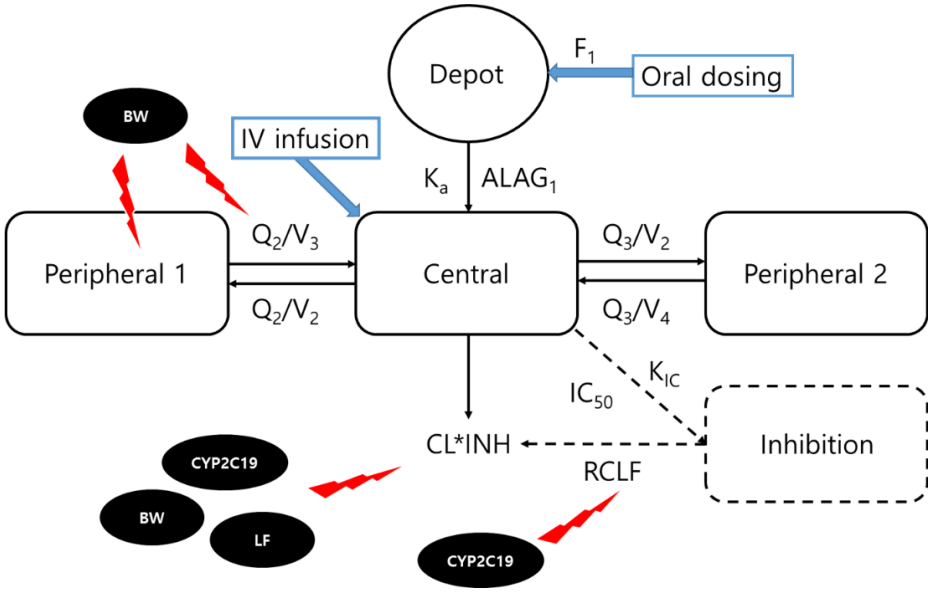


**Figure 1.** Structure of the population pharmacokinetic model for voriconazole concentrations and significant covariates. Clearance (CL) is inhibited based on the concentration in an empirical inhibition compartment. $C_{Inh}$ corresponds to the concentration in the inhibition compartment. INH corresponds to [RCLF + (1 − RCLF) × (1 − $C_{Inh}$ / ($IC_{50}$ + $C_{Inh}$))]. $F_1$, bioavailability; $K_a$, absorption rate constant; $ALAG_1$, absorption lag−time; $V_2$, central volume of distribution; $Q_2$ and $Q_3$, inter−compartmental clearance; $V_3$ and $V_4$, peripheral volume of distribution; $K_{IC}$, rate constant into inhibition compartment; RCLF, remaining CL fraction, i.e., fraction of clearance which cannot be inhibited; $IC_{50}$, concentration in the inhibition compartment yielding 50% of maximum clearance inhibition; IV, intravenous; BW, body weight; LF, liver function.

**Table 3.** Parameter estimates of the final population pharmacokinetic model.

| Parameters | Estimates | RSE (%) |
|---|---|---|
| **Structural model** | | |
| $V_2$; central volume of distribution (L) | 35.7 | 15.7 |
| CL; clearance (L/h) | 45.3 | 5.8 |
| $V_3$; peripheral 1 volume of distribution (L) | 58.9 | 6.2 |
| $Q_2$; inter-compartmental clearance between central and peripheral 1 compartment (L/h) | 10.9 | 8.0 |
| $V_4$; peripheral 2 volume of distribution (L) | 25.4 | 16.7 |
| $Q_3$; inter-compartmental clearance between central and peripheral 2 compartment (L/h) | 54.6 | 45.4 |
| $K_a$; absorption rate constant ($h^{-1}$) | 1.23 | 15.4 |
| $F_1$; bioavailability | 0.876 | 2.3 |
| $ALAG_1$; absorption lag-time (h) | 0.237 | 1.8 |
| RCLF; fraction of clearance which cannot be inhibited | 0.162 | 9.7 |
| $IC_{50}$; concentration in the inhibition compartment yielding 50% of maximum clearance inhibition | 0.01 FIX | NA |
| $K_{IC}$; rate constant into inhibition compartment | 0.002 | 14.9 |
| **Inter-individual variability (IIV)** | | |
| IIV for $V_2$ (% CV) | 40.2 | 23.3 [a] |
| IIV for CL (% CV) | 21.4 | 10.6 [a] |
| IIV for $V_3$ (% CV) | 20.6 | 34.1 [a] |
| IIV for $Q_2$ (% CV) | 28.8 | 20.0 [a] |
| IIV for $K_a$ (% CV) | 87.8 | 14.4 [a] |
| IIV for $F_1$ (% CV) | 84.4 | 20.3 [a] |
| IIV for RCLF (% CV) | 54.4 | 13.0 [a] |
| Correlation between $V_2$ and CL | 0.0116 | 95.7 [b] |

| | | |
|---|---|---|
| Correlation between $V_2$ and $V_3$ | −0.0117 | 200.9 [b] |
| Correlation between $V_2$ and $Q_2$ | −0.0734 | 49.2 [b] |
| Correlation between CL and $V_3$ | −0.0119 | 72.5 [b] |
| Correlation between CL and $Q_2$ | 0.008 | 150.3 [b] |
| Correlation between $V_3$ and $Q_2$ | 0.0345 | 67.0 [b] |
| Residual variability | | |
| Additive error for healthy subjects (mg/L) | 0.208 | 8.4 |
| Additive error for patients (mg/L) | 0.799 | 6.7 |

RSE, relative standard error; NA, not applicable; [a] Standard error given on the variance scale; [b] Standard error of the covariance estimate.

In the final model, several covariates that significantly affected the pharmacokinetics of voriconazole were identified (Table 4). As we expected, the CYP2C19 phenotype significantly affected the pharmacokinetics of voriconazole. The CL of voriconazole decreased by 17% (37.6 L/h) and 53% (21.5 L/h) in the CYP2C19 IMs and PMs respectively compared to that in the CYP2C19 EMs (45.3 L/h). Furthermore, the RCLF also decreased by approximately 36–40% (0.097–0.104) in the CYP2C19 IMs and PMs, compared to that in the CYP2C19 EMs (0.162). Accordingly, the final model accurately predicted the time-dependent CL change, which showed the different magnitude of change in accordance with the CYP2C19 phenotypes (Figure 2). Regardless of CYP2C19 phenotypes, inhibition of voriconazole CL was identified to reach the steady state from approximately 72 hours. In addition, body weight was found to be a significant covariate of CL, peripheral volume of distribution ($V_3$), and inter-compartmental clearance ($Q_2$) of voriconazole. A significant reduction (53%) in voriconazole CL was also observed in patients with liver dysfunction (grade ≥ 3), which indicated that these patients might be at a higher risk of exceeding the target range of voriconazole concentration.

**Table 4.** Significant covariate effects on the population pharmacokinetic parameters in the final model.

| Variable | Estimates | RSE (%) |
|---|---|---|
| **Effect on CL** | | |
| Body weight exponent for CL | 0.595 | 31.8 |
| CYP2C19 phenotype effect for CL (cf. 0 for extensive metabolizer) | | |
| Intermediate metabolizer | −0.186 [a] | 29.5 [a] |
| Poor metabolizer | −0.746 [a] | 10.9 [a] |
| Liver function abnormality effect for CL (cf. 0 for grade < 3) | | |
| Grade ≥ 3 | −0.75 | 49.3 |
| **Effect on $V_3$** | | |
| Body weight exponent for $V_3$ | 2.2 | 20.0 |
| **Effect on $Q_2$** | | |
| Body weight exponent for $Q_2$ | 2.56 | 18.1 |
| **Effect on RCLF** | | |
| CYP2C19 phenotype effect for RCLF (cf. 0 for extensive metabolizer) | | |
| Intermediate metabolizer | −0.51 [a] | 27.5 [a] |
| Poor metabolizer | −0.44 [a] | 42.3 [a] |

RSE, relative standard error; CL, clearance; $V_3$, peripheral 1 volume of distribution; $Q_2$, inter−compartmental clearance between central and peripheral 1 compartment; RCLF, fraction of clearance which cannot be inhibited; [a] The values were estimated using healthy subject data.

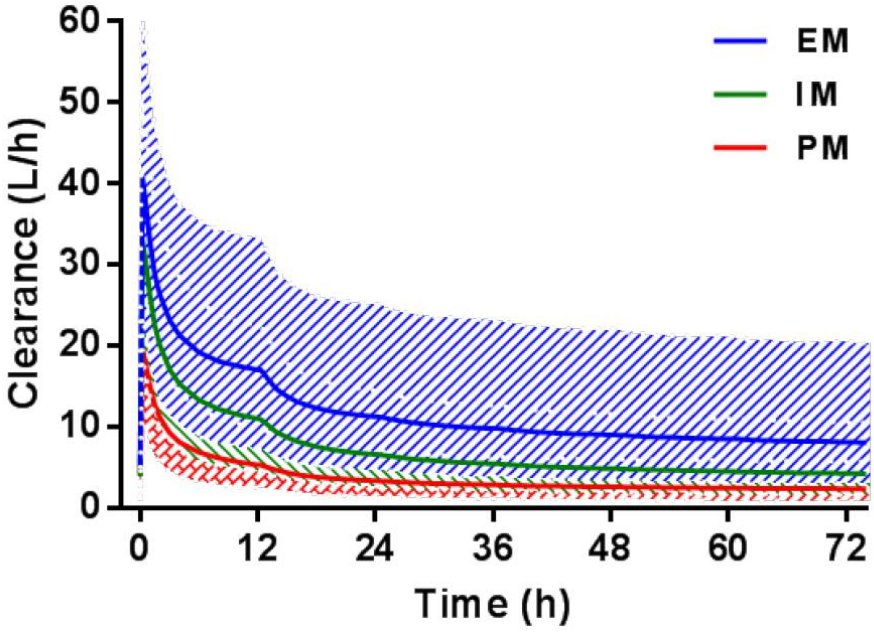


Figure 2. Predicted voriconazole clearance versus time after oral dosing of 400 mg twice daily for two doses followed by 200 mg twice daily

## Model Validation

The basic goodness of fit (Figure 3) and pcVPC plots (Figure 4) showed a good predictive performance of the developed model and indicated that the model appropriately described the observed voriconazole concentrations in accordance with the CYP2C19 phenotypes and the route of administration of voriconazole. For numerical quantification of the predictive performance for the patient data, the mean bias and precision (MPE and RMSE, respectively) were observed to be well below 25% and remained relatively constant throughout the observations with different CYP2C19 phenotypes (Table 5). Simulation-based model diagnostics using NPDE showed that the data points were not systematically deviated from the horizontal zero-line with no trends when plotted versus population predictions and time, and most of the points lie within the range from -1.96 to 1.96. (Figure 5).

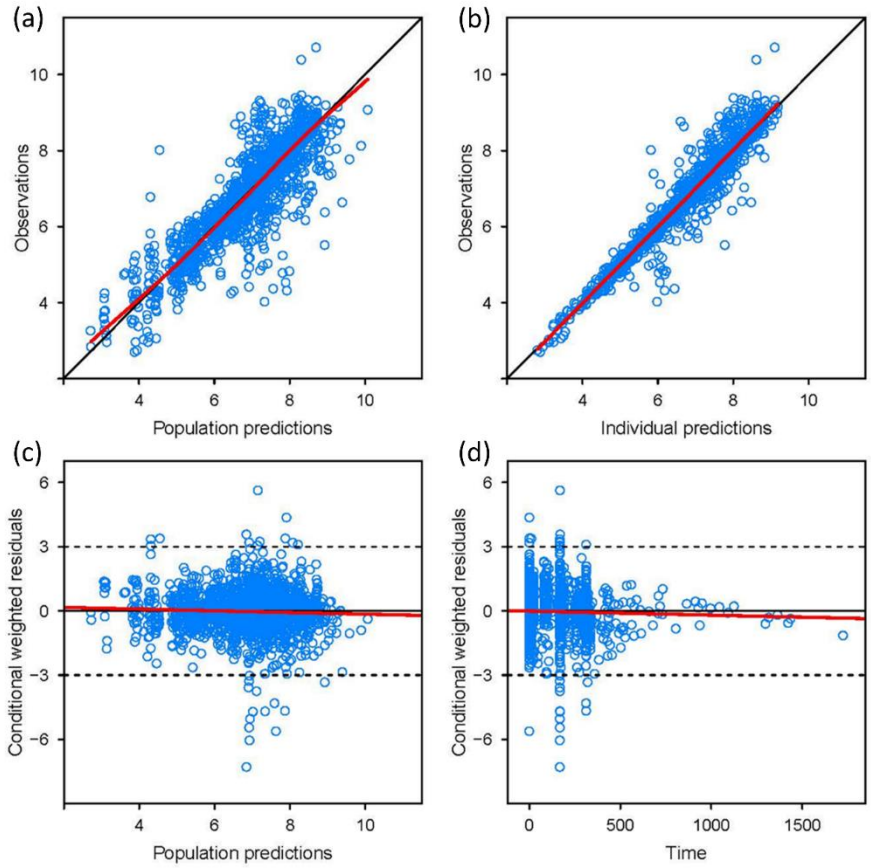


**Figure 3.** Basic goodness-of-fit plots of final population pharmacokinetic model for voriconazole. (a) observations versus population predictions; (b) observations versus individual predictions; (c) conditional weighted residuals versus population predictions; (d) conditional weighted residuals versus time

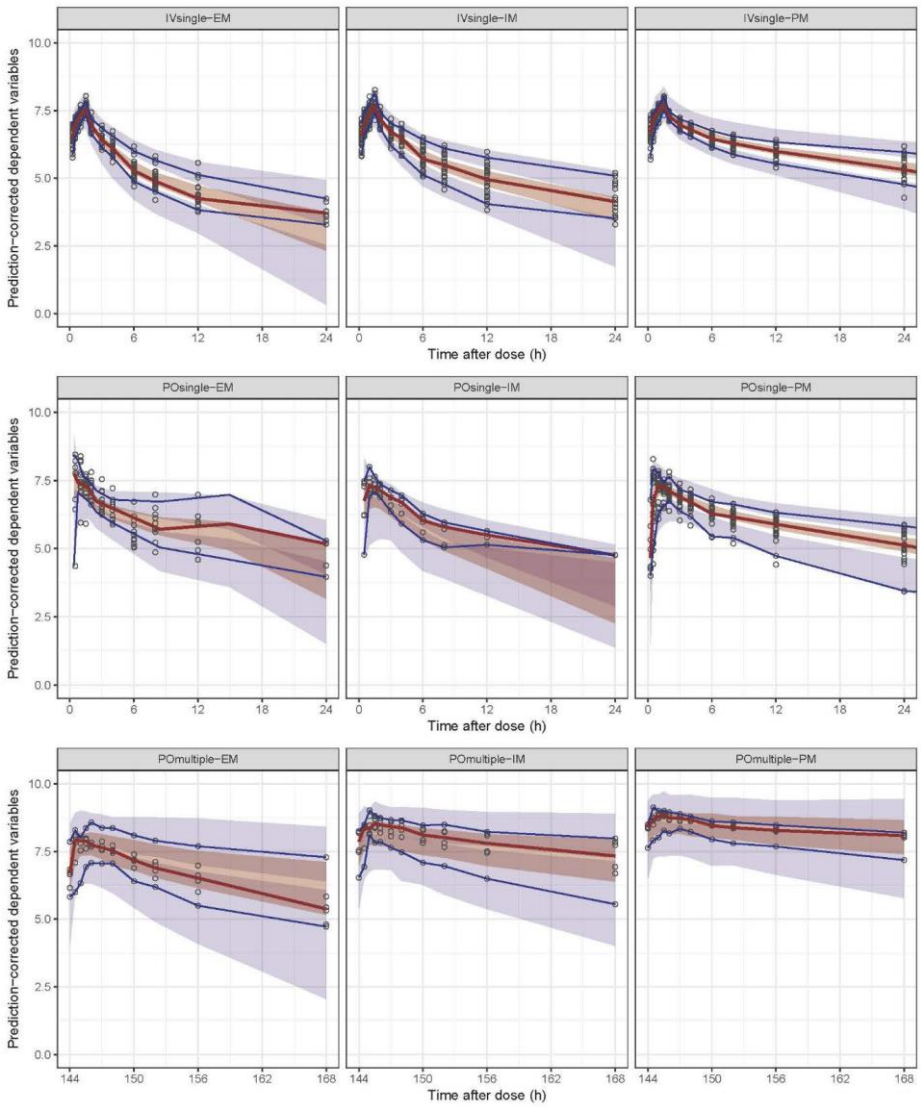


**Figure 4.** Prediction−corrected visual predictive check for healthy subject data in the final pharmacokinetic model. The circles represent the observed concentrations. The lines represent the median (red) and the 5$^{th}$ and 95$^{th}$ percentiles (blue) of the observed concentration. The areas represent the 95% confidence intervals for the median (red) and 90% prediction interval (blue) of the simulated concentrations.

Table 5. Predictive performance of voriconazole pharmacokinetic model for the data from the patients

| | N[a] | Bias and imprecision | |
|---|---|---|---|
| | | MPE (%)[b] | RMSE (%)[c] |
| Total | 249 | 2.0 (−0.6, 4.6) | 20.7 |
| CYP2C19 EM | 113 | −2.8 (−6.8, 1.3) | 21.9 |
| CYP2C19 IM | 104 | 4.6 (0.8, 8.5) | 20.4 |
| CYP2C19 PM | 32 | 10.3 (5.5, 15.2) | 17.2 |

[a] N represents the number of observations

[b] Data in parentheses are 95 % confidence intervals; MPE, mean prediction error;

[c] RMSE, relative root mean squared error

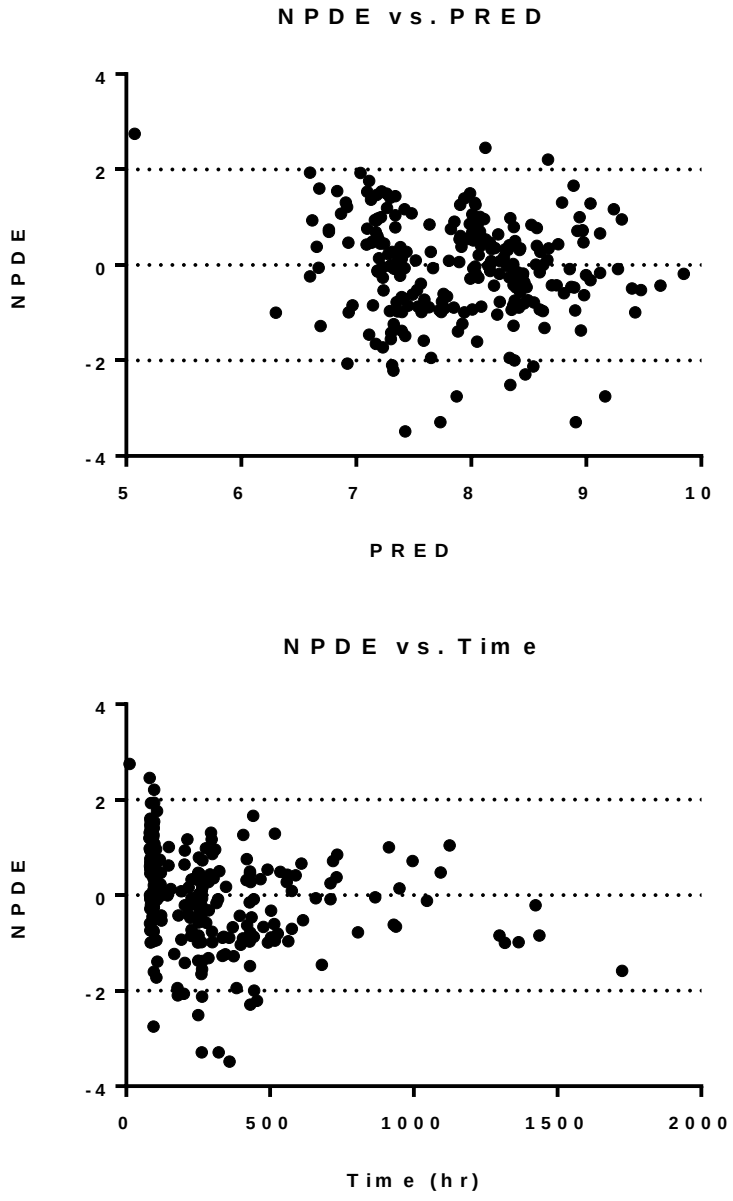


Figure 5. Scatterplots of normalized prediction distribution error (NPDE) vs. population prediction (PRED) or time for the patients' data

## Various Dosing Regimens According to the CYP2C19 Phenotypes

Based on the final population pharmacokinetic model, the concentration-time profiles of voriconazole after 7-day multiple oral doses of standard dosing regimen (400 mg twice daily for two doses followed by 200 mg twice daily) were simulated according to the CYP2C19 phenotypes (Figure 6). On average, the trough concentrations after 7-day dosing seemed to reach within the target trough range of 2.0–5.5 mg/L. However, when classified according to the CYP2C19 phenotypes, the trough concentrations reached mostly below the target range in the subjects with EM, while the trough concentrations in the subjects with PM were higher than the target range. Likewise, the evaluation of the probability of voriconazole therapeutic target attainment by the standard oral dosing regimen showed that only 38.9% of the subjects' concentration fell within the therapeutic target range. The probabilities of subtherapeutic concentration attainment were high (73.9%) in the subjects with EM, while the subjects with PM showed high toxic concentration attainment (48.3%), suggesting the need for dose adjustment according to the CYP2C19 phenotypes (Figure 7a, Table 6).

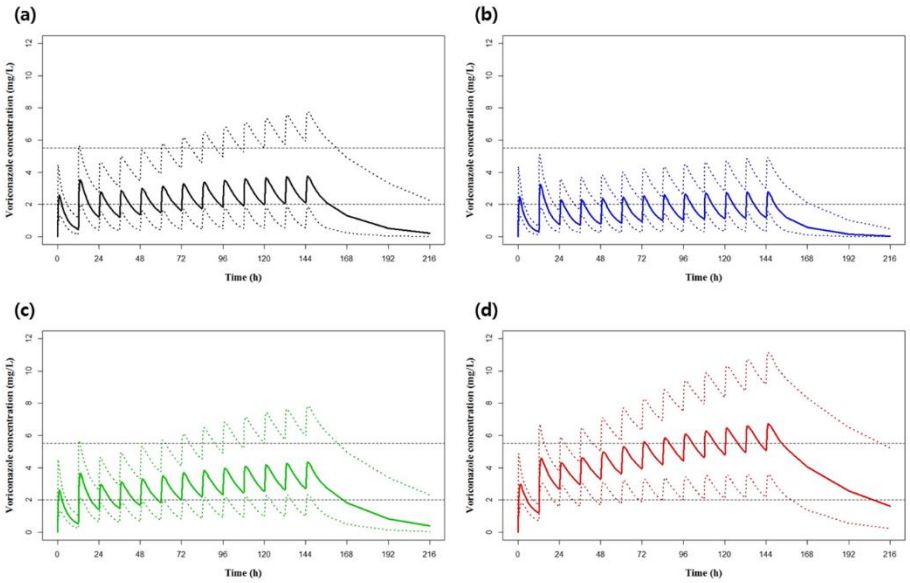


Figure 6. Predicted median concentration–time profile over the first 7 days of treatment of (a) total 10,000 simulated patients or patients with (b) CYP2C19 EM phenotype, (c) IM phenotype, and (d) PM phenotype. Standard oral dosing (400 mg twice daily for two doses followed by 200 mg twice daily) was used. The solid lines represent the median, with the dotted lines representing the $10^{th}$ and $90^{th}$ percentiles. The dashed lines represent the therapeutic target range for voriconazole trough plasma concentration of 2.0 to 5.5 mg/L.

In order to derive an appropriate dosing regimen for each CYP2C19 phenotype, we evaluated the therapeutic target attainments for the various oral dosing regimens (Table 6), and suggested the optimal dosing regimens to achieve the highest probability of reaching the therapeutic concentration as follows; EM: 400 mg twice daily, IM: 400 mg twice daily for two doses followed by 200 mg twice daily, and PM: 400 mg twice daily for two doses followed by 100 mg twice daily. The optimal dosing regimen resulted in higher probabilities of therapeutic target attainment in each CYP2C19 phenotype (i.e., 44.7%, 52.9%, and 58.1% for EM, IM, and PM respectively) compared to the standard dosing regimen (i.e., 23.3%, 52.9%, and 43.7%). In addition, the probability of subtherapeutic concentration attainment in the subjects with EM and the probability of toxic concentration attainment in the subjects with PM significantly decreased by the suggested CYP2C19 phenotype-guided dosing (i.e., 37.8% and 10.3%, respectively; Figure 7b, Table 6).

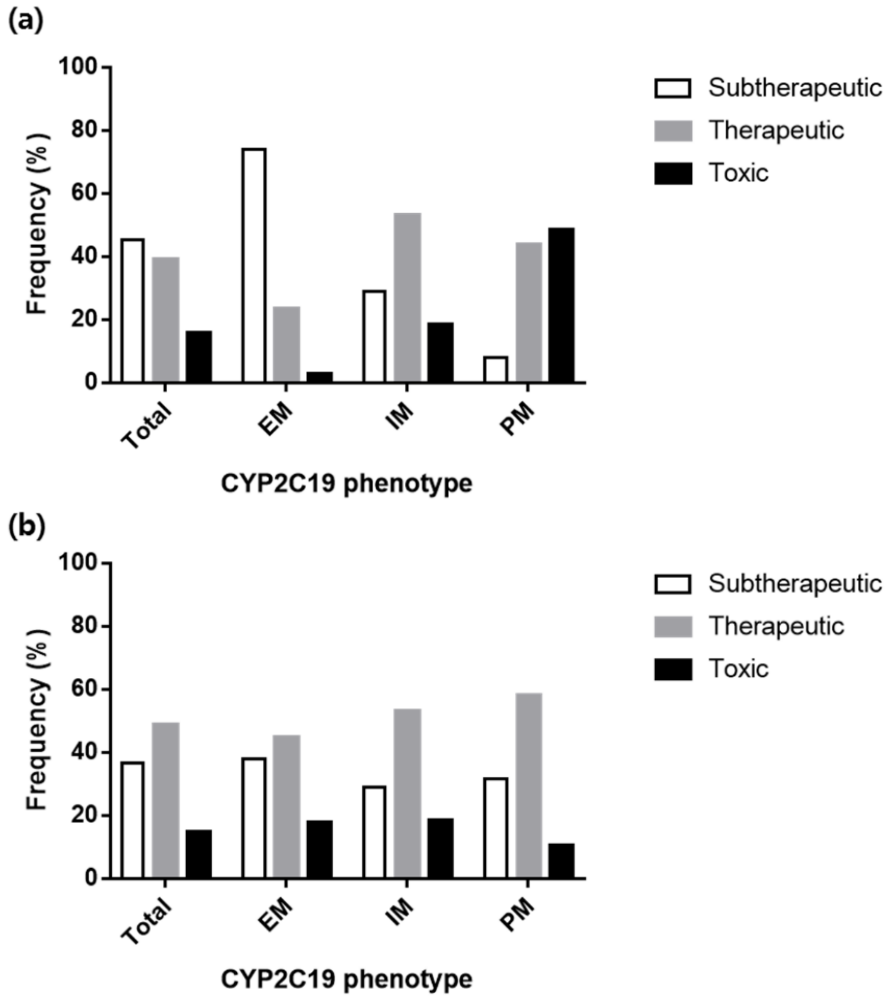


Figure 7. Probability of voriconazole therapeutic target attainment from model-based simulations of voriconazole pharmacokinetic profiles after the following voriconazole oral dosing regimens on day 7; (a) standard dosing regimen (400 mg twice daily for two doses followed by 200 mg twice daily), (b) dosing according to CYP2C19 phenotype as follows: EM, 400 mg twice daily; IM, 400 mg twice daily for two doses followed by 200 mg twice daily; PM, 400 mg twice daily for two doses followed by 100 mg twice daily. Therapeutic target range for voriconazole trough plasma concentration was from 2.0 to 5.5 mg/L.

Table 6. Probabilities of target attainment on day 7 from model-based simulations of voriconazole pharmacokinetic profiles after 400 mg twice daily for two doses followed by various voriconazole oral dosing regimens

| CYP2C19 Phenotype | Target attainment | 100 mg BID | 150 mg BID | 200 mg BID | 250 mg BID | 300 mg BID | 350 mg BID | 400 mg BID |
|---|---|---|---|---|---|---|---|---|
| EM | Subtherapeutic | 95.1 | 86.1 | 73.9 | 61.9 | 51.9 | 45.6 | 37.8 |
| | Therapeutic | 4.8 | 13.0 | 23.3 | 32.8 | 39.0 | 41.6 | 44.7 |
| | Toxic | 0.1 | 0.9 | 2.8 | 5.3 | 9.1 | 12.9 | 17.5 |
| IM | Subtherapeutic | 69.3 | 46.0 | 28.8 | 18.7 | 13.9 | 10.3 | 6.2 |
| | Therapeutic | 28.9 | 46.7 | 52.9 | 51.1 | 46.2 | 38.6 | 35.5 |
| | Toxic | 1.8 | 7.3 | 18.3 | 30.2 | 39.9 | 51.1 | 58.3 |
| PM | Subtherapeutic | 31.6 | 14.9 | 8.0 | 3.8 | 2.4 | 1.4 | 0.8 |
| | Therapeutic | 58.1 | 57.1 | 43.7 | 32.9 | 24.6 | 18.4 | 13.3 |
| | Toxic | 10.3 | 28.0 | 48.3 | 63.4 | 73.0 | 80.2 | 85.9 |
| Total | Subtherapeutic | 75.1 | 58.9 | 45.3 | 35.2 | 28.6 | 24.2 | 19.0 |
| | Therapeutic | 22.6 | 33.7 | 38.9 | 40.7 | 40.1 | 37.1 | 36.3 |
| | Toxic | 2.3 | 7.4 | 15.8 | 24.1 | 31.3 | 38.8 | 44.6 |

BID, twice daily

# DISCUSSION

The present study was performed to develop a population pharmacokinetic model of voriconazole, taking into account the clinically important covariates, including the CYP2C19 phenotype, and to evaluate the appropriateness of various dosing regimens according to the CYP2C19 phenotypes. This study is scientifically meaningful because the population pharmacokinetic analysis included a sufficient number of subjects whose CYP2C19 phenotypes were all identified, and there was a sufficient number of subjects with intensive pharmacokinetic sampling, which derived the robust and proper population pharmacokinetic model. This study is also worthwhile, as the developed model is the first mechanistic model incorporating the auto-inhibitory characteristic of voriconazole to illustrate its non-linear pharmacokinetic characteristics with time-dependent elimination. Through this study, we quantitatively identified the effects of the CYP2C19 genotype on voriconazole pharmacokinetics and eventually suggested an optimal dosing regimen based on that.

The developed mechanism-based model explains the non-linear pharmacokinetic profile of voriconazole better than the

previous models. So far, the elimination of voriconazole has been described as a linear [27, 28], non-linear [29-31], or mixed (linear and non-linear) [32, 33] process. The underlying mechanism of the non-linear pharmacokinetic property of voriconazole is supported by its CYP-mediated auto-inhibition and saturation of its own metabolism [12, 34], which made our modeling approach reasonable. In addition, richly sampled pharmacokinetic data from the healthy volunteers helped to develop a robust model and overcome the disturbances from sparse data obtained from the patients. Therefore, it was possible to determine the accurate elimination profile of voriconazole that reflects the mechanistic auto-inhibition characteristics properly.

Among the various covariates affecting the pharmacokinetics of voriconazole, the CYP2C19 phenotype, a major factor that contributes to the high variability of voriconazole exposure was identified as a clinically significant covariate for both CL and RCLF. In the present study, the CL of voriconazole decreased by 17% (37.6 L/h) and 53% (21.5 L/h) in the CYP2C19 IMs and PMs respectively compared to that in the EMs (45.3 L/h). This result was relatively consistent with some previous studies

showing 37% reduction of the linear CL in CYP2C19 PMs [28], and approximately 40% reductions of the maximum rate of metabolism ($V_{max}$) in non-linear (Michaelis-Menten) kinetics in CYP2C19 IMs/PMs or PMs [30, 33]. However, these reports had some limitations due to the relatively small number of subjects included for the analysis or the fact that it was not possible to evaluate all the CYP2C19 phenotypes evenly.

The RCLF of voriconazole, which indicates the remaining CL fraction at a steady state, was adopted to the model to illustrate its non-linear pharmacokinetic characteristics with time-dependent elimination by its auto-inhibitory characteristic. From a mechanistic perspective, the decrease in CL is caused by the RCLF parameter, explaining the magnitude of the auto-inhibition profile due to the voriconazole itself and the voriconazole major N-oxide metabolite. It is reported that CYP3A4 is significantly inhibited by voriconazole to a larger portion than CYP2C19. From an *in vitro* result, voriconazole $K_i$ for competitive inhibition of CYP3A4 metabolism is 0.66 $\mu$mol/L and 2.97 $\mu$mol/L for non-competitive CYP3A4 inhibition, and voriconazole can be also a moderate competitive inhibitor of CYP2C19 ($K_i$ = 5.1 $\mu$mol/L) [10]. In addition, the proportion of N-oxide mediated CYP3A4

inhibition is likely to be small ($IC_{50}$ = 146 $\mu$mol/L) but larger for CYP2C19 inhibition ($IC_{50}$ = 40.2 $\mu$mol/L) [11]. Based upon this information, after achieving full magnitude of auto-inhibition at steady-state, CYP2C19-mediated metabolism (along with flavin containing monooxygenases (FMOs) and possibly CYP2C9) and renal clearance are the remaining elimination pathway. Therefore, the remaining CYP2C19-mediated metabolism can be the key determinant of voriconazole exposure. If this metabolism is also decreased (for example, due to poor metabolizing enzymes), then voriconazole concentration will be increased more significantly, which supports that the auto-inhibition profile can be different according to CYP2C19 phenotypes.

In this study, the time-dependent CL of voriconazole was identified to show different extent according to the CYP2C19 phenotypes. The RCLF decreased by approximately 36-40% (0.097-0.104) in the CYP2C19 IMs or PMs, compared to that in the EMs (0.162). This signifies that when the steady-state is reached, the time-dependent CL changes from 45.3 to 7.3 L/h in CYP2C19 EMs, from 37.6 to 3.9 L/h in IMs, and from 21.5 to 2.1 L/h in PMs respectively (Table 4, Table 4 and Figure 2). Although there has not been any report with the IMs and/or PMs,

the result with the EMs was consistent with a previous study which reported approximately 80% reduction of $V_{max}$ at the steady state in CYP2C19 Ultrarapid metabolizers/EMs [32]. The time-dependent inhibition characteristic is a key factor to understand the non-linear pharmacokinetics of voriconazole. Therefore, it is important to consider not only the simple change in voriconazole CL but also the change in CL over time according to the CYP2C19 genotypes. To the best of our knowledge, the present study is the first study to quantitatively identify the effect of each CYP2C19 phenotype on CL, as well as on RCLF.

In addition to the CYP2C19 phenotype, several other covariates were identified which need to be considered during the clinical use of voriconazole. Among them, liver dysfunction significantly affected the CL of voriconazole, demonstrating up to 53% reduction of CL in patients with grade ≥ 3 of liver dysfunction (Table 4). This result can be supported by the recommended maintenance dose to be reduced in patients with mild to moderate hepatic insufficiency (Child-Pugh Class A and B), which is halved due to 3.2-fold higher mean AUC of voriconazole than that in controls with normal hepatic function [34]. It was also reported by some previous studies that severe

hepatic cholestasis significantly lowers the voriconazole CL by approximately 10%, and the CL was reduced by 16% as alkaline phosphatase level increased by 100 (U/L) [27, 28]. However, further evaluation is needed due to the limited data available from only 6 patients with grade ≥ 3 hepatic abnormality in this study. In addition, body weight was identified as a significant covariate of the CL, $V_3$, and $Q_2$, although the influence of body weight was not sufficient to change the voriconazole dosing regimen, which was supported by several studies showing no relationship between body weight and voriconazole pharmacokinetics [27, 28, 30]. It is inconsistent with the prescribing information of voriconazole, which recommends that the oral maintenance dose should be 100 or 150 mg for adult patients weighing less than 40 kg [34]. This might occur because there was no patient with a body weight of less than 40 kg in our study.

In the present study, none of the co-medications (PPIs and glucocorticoids) was identified as a significant covariate on voriconazole exposure. In contrast, recent studies have reported the exposure of voriconazole increased to varying degrees depending on the kinds of PPIs used [35, 36], although, the role of glucocorticoids on voriconazole exposure remains

controversial [19, 30, 36–38]. Some of previous studies reported that co–medication of glucocorticoids induced lower voriconazole exposure supported by an inductive effect on CYP2C19 and/or CYP3A, while others have shown different results. This inconsistency in this study may be because of the small number of patients who had taken those concomitant medications with sparse pharmacokinetic data and different underlying conditions of the patients, which warrants further studies to confirm. Although the effects of PPIs and glucocorticoids on voriconazole exposure have not been yet confirmed, an attention should be granted by clinicians since concomitant administration of voriconazole and PPIs and/or glucocorticoids to patients is used commonly in clinical practice.

In the clinical settings, the standard dosing regimen of voriconazole has been suggested as an oral dose of 400 mg bid for two doses followed by 200 mg bid for adults regardless of the CYP2C19 phenotypes [34]. Based on the results of this study, the suggested CYP2C19 genotype–guided oral dosing regimen to maximize the probability of timely achieving the therapeutic range of 2.0–5.5 mg/L is 400 mg bid for two doses followed by 400 mg bid in the EMs, 200 mg bid in the IMs, or 100 mg bid in

the PMs. The suggested dose for CYP2C19 EMs appears to be slightly higher than the conventional dose because the target trough range is higher than the conventional range (0.5–5.5 mg/L) [39, 40]. From a different point of view, other proposed regimens that maximize the probability of achieving the therapeutic concentration while keeping attainment of the probability of toxic concentration under 20% are as follows: 400 mg bid for two doses, followed by 300–400 mg bid for the EMs, 400 mg bid for two doses followed by 150–200 mg bid for the IMs, and 400 mg bid for two doses followed by 100 mg bid for the PMs (Table 6). Although we could not evaluate the potential effect of *17 on voriconazole exposure due to only one patient having *17 included for the analysis, there is a need for further study to confirm. Because a previous report showed that higher doses of voriconazole are needed to maximize the benefit for CYP2C19 rapid metabolizer (*1/*17) and ultrarapid metabolizer (*17/*17) [41]. In the clinical setting, one of the variously proposed dosing regimens can be selected based on the patient's condition, taking into account the likelihood of therapeutic success and the risk of adverse effects.

Despite the potential use of the proposed CYP2C19

genotype-guided oral dosing regimen, challenges still remain in real life situations [15]. There are difficulties in obtaining the CYP2C19 genotype of the patients before initiating voriconazole therapy due to the time and cost associated with the laboratory process. In case of our hospital, Seoul National University and Hospital, it takes three weeks to identify the CYP2C19 genotype and the cost of genotyping assay is $328, which means that it is the time- and cost-burden procedure for both clinicians and patients. Considering this, TDM is a good alternative to genotyping for voriconazole dosing, for which TDM is cheaper and timely approachable procedure than genotyping. However, a previous budget impact study has reported that the proactive CYP2C19-guided voriconazole prophylaxis in acute myelogenous leukemia patients can have moderate cost saving ($415 per patient) as well as improving outcomes for the treatment [42]. In addition, the pharmacokinetics of voriconazole require at least five to seven days of dosing prior to achieving an adequate steady-state concentration. Thus, poor or rapid metabolizers could be over- or under-dosed for over a week before dose adjustment achieve adequate treatment outcome. Preventing from serious adverse reactions or invasive fungal

infection during this period by identifying genotype information would be less expensive than TDM in terms of a total time- and cost-perspective, which needs to be confirmed through a valid cost-effectiveness analysis. In addition, a strong consensus for therapeutic range and dosing regimen of voriconazole has not been reached yet. These limitations can be compensated by the CYP2C19 genotype-guided dosing in patients with available CYP2C19 genotype followed by TDM-guided dose adjustments for refining the dose due to a number of still existing factors affecting variability in addition to CYP2C19 genotype. In the future, it is necessary to develop an individualized optimal dosing regimen of voriconazole considering various factors including genotypes.

In this research, we could observe large unexplained residual variability (within-subject variability) as population-dependent errors especially in the patient population (~80%) (Table 3). Patient data was collected from a randomized controlled clinical study, which consists of trough levels of voriconazole 4 days after treatment initiation. There were several possible reasons for this high variability in the patient. First of all, clinical conditions of the patients and concomitant medications were

different. In addition to fungal infection, most of them were diagnosed with hematologic diseases resulting in different number of absolute neutrophil counts, but some of them were having other types of cancers, kidney transplantation, rheumatoid arthritis, systemic sclerosis, hypertension, diabetes, pneumonia, tuberculosis, and so on. Different clinical conditions accompany different kinds of concomitant medications required, which may affect the pharmacokinetics of voriconazole. Second, we could not obtain the genotype information of minor pathways of metabolizing enzymes including CYP3A4/5, CYP2C9, and the members of the FMO family. The CYP enzymes influence approximately 75% of the voriconazole metabolism, while the FMO family mediates the remaining 25% [43]. Therefore, reduced function of these minor influencing enzymes may have contributed to the large residual variability in this study. Third, some of the pharmacokinetic sampling points were not exactly the time for the trough levels. Due to the unpredictable clinical situations, some points were obtained before and after trough levels and hemodialysis, or even during the infusion of voriconazole, or just missing.

There are a few limitations in this study. First, metabolite

concentrations of voriconazole were not included for the analysis. Considering that both voriconazole and its metabolite can affect voriconazole CL by inhibiting own metabolism, we could have explained the mechanistic impact better when incorporating the metabolite concentrations into the analysis. Second, there were limited subjects having rapid or ultrarapid metabolizers for CYP2C19 genotype, so that we could not evaluate the potential effect on voriconazole pharmacokinetics and ultimately derive the optimal dosing regimens of voriconazole for the fast metabolizers. However, in Asian population, since CYP2C19 variants exist in a relatively large proportion compared to Caucasian population, this study could better identify the effects of variants having greater risk of toxicity. Third, there is a possibility that a slight bias may be caused to the pharmacokinetic parameters because the voriconazole concentrations below the lower limit of quantification were omitted instead of handling these data in a proper method. Lastly, as I mentioned above, we could not obtain the genotype information of minor pathways of metabolizing enzymes including CYP3A4/5, CYP2C9, and the members of FMO family. Probability of reduced function of these enzymes that might affect the

voriconazole pharmacokinetics still remains in the unexplained residual variability.

# CONCLUSION

In conclusion, the pharmacokinetic parameters of voriconazole were well described by the developed population pharmacokinetic model. This was the first attempt to mechanistically explain the non-linear pharmacokinetics of voriconazole using an inhibition compartment model with incorporation of CYP2C19 phenotype effect. The proposed CYP2C19-guided initial dosing regimen based on the final model will provide a rationale to individualize optimal dosing to improve clinical outcomes with voriconazole therapy.

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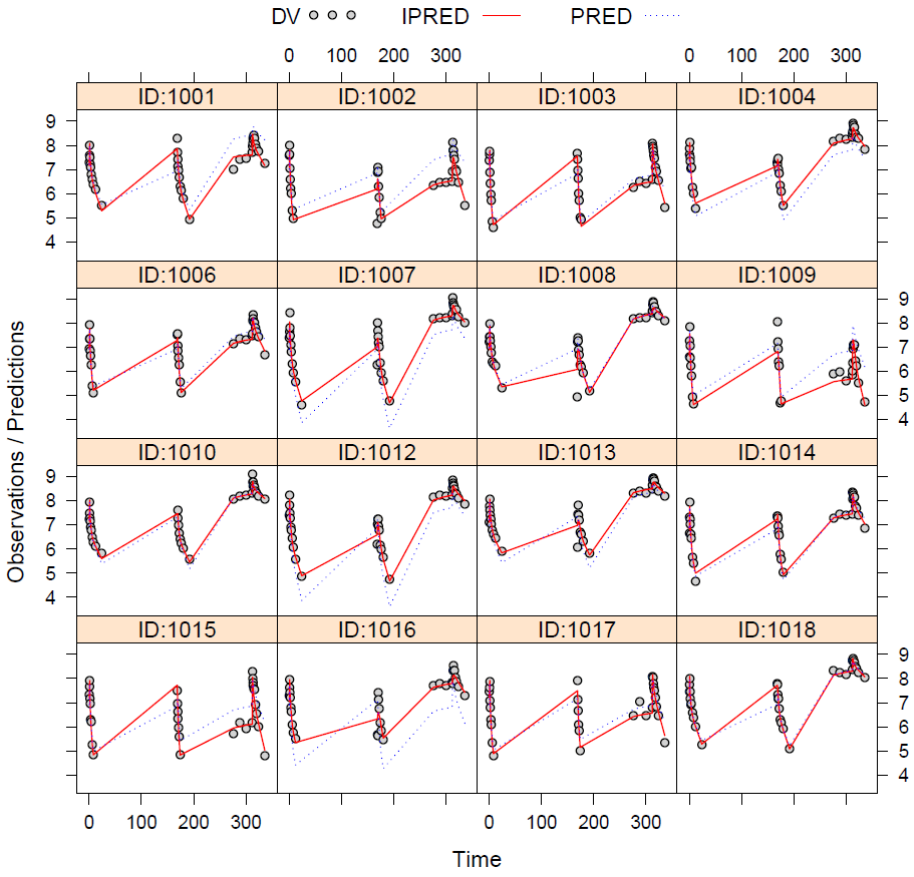
# APPENDICES

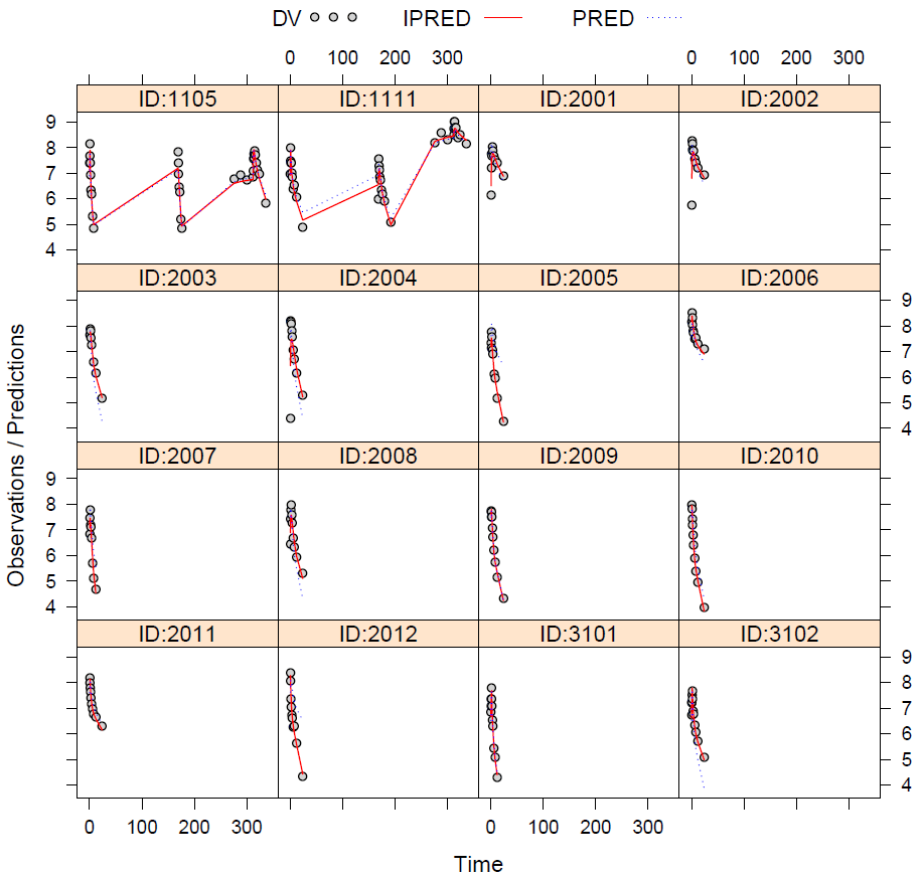
## 1. Individual fitting plot for the final pharmacokinetic model

Study 1: ID 1001−1111, Study 2: ID 2001−2012, Study 3: ID 3101−3230, Study 4: ID 4101−4206, Study 5: ID 5003−5110



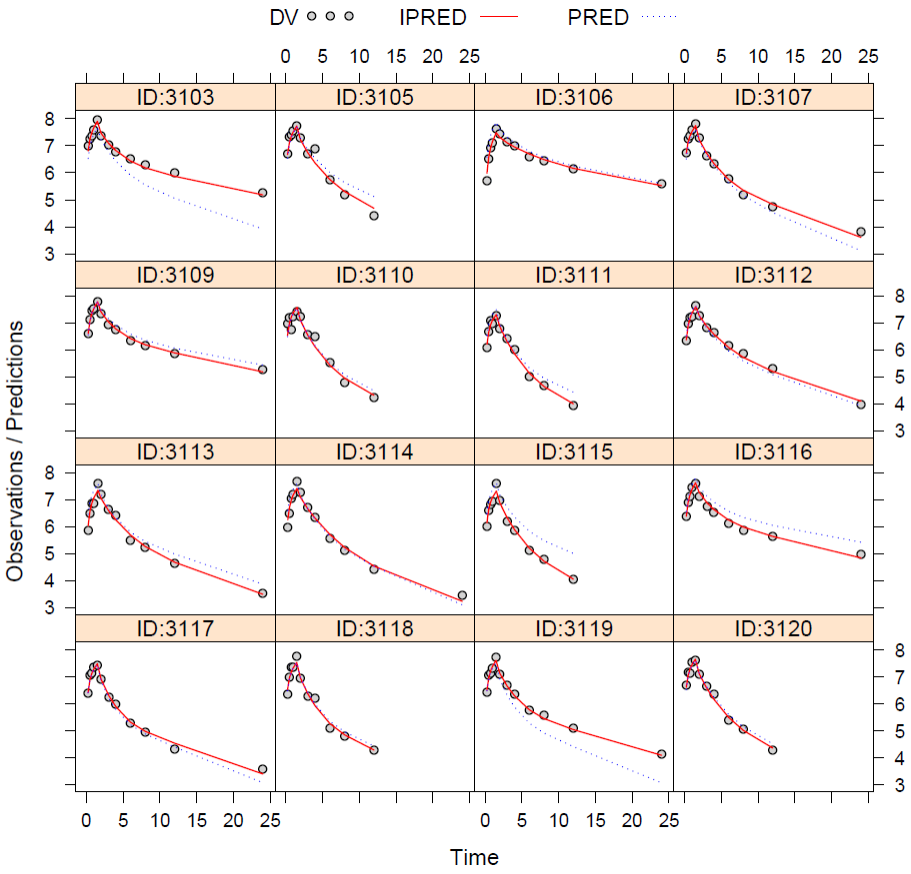
Individual fitting plot for the final pharmacokinetic model (Continued)

Study 1: ID 1001−1111, Study 2: ID 2001−2012, Study 3: ID 3101−3230, Study 4: ID 4101−4206, Study 5: ID 5003−5110



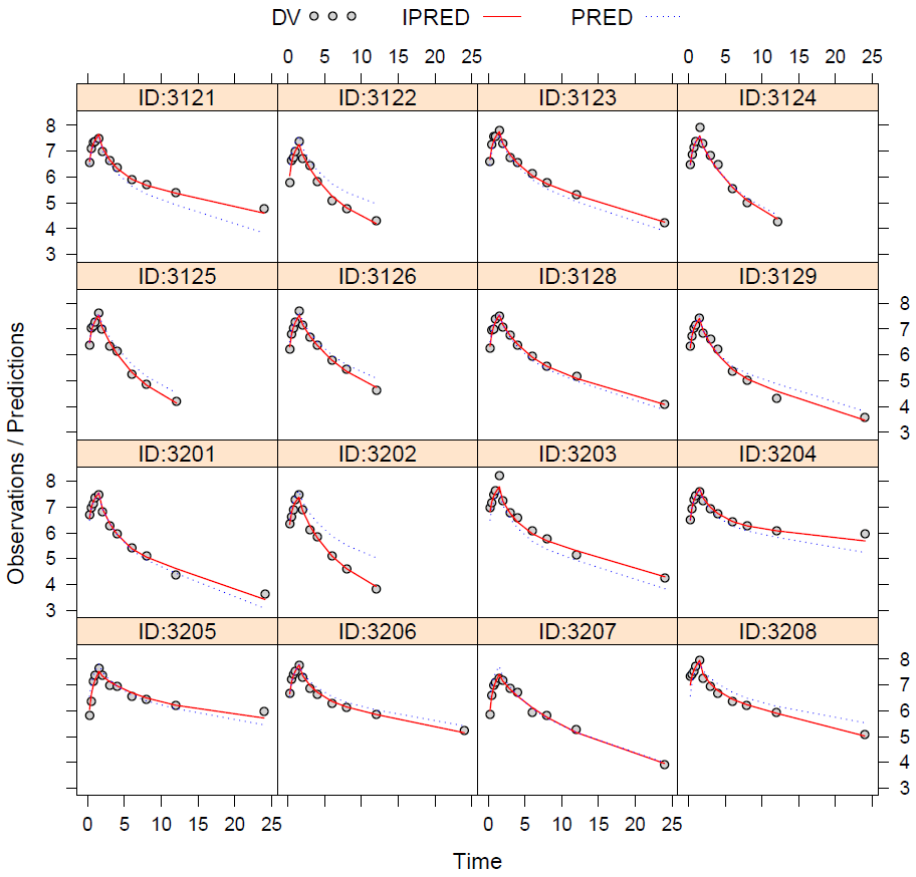
Individual fitting plot for the final pharmacokinetic model (Continued)

Study 1: ID 1001−1111, Study 2: ID 2001−2012, Study 3: ID 3101−3230, Study 4: ID 4101−4206, Study 5: ID 5003−5110



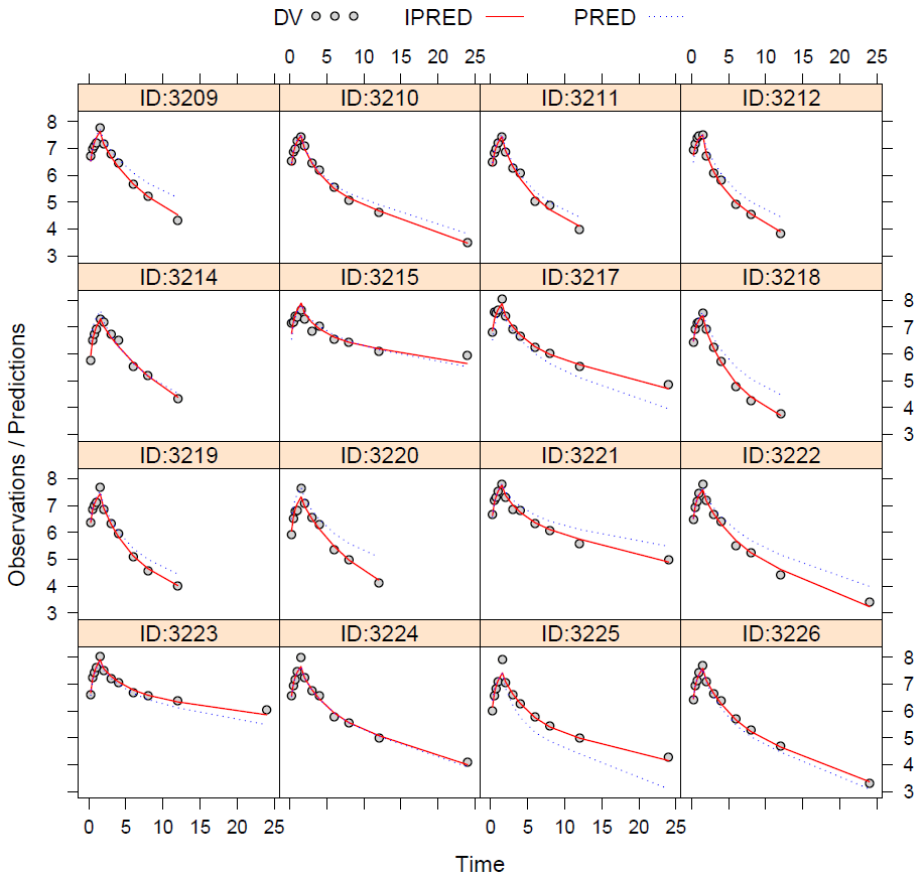
Individual fitting plot for the final pharmacokinetic model (Continued)

Study 1: ID 1001−1111, Study 2: ID 2001−2012, Study 3: ID 3101−3230, Study 4: ID 4101−4206, Study 5: ID 5003−5110



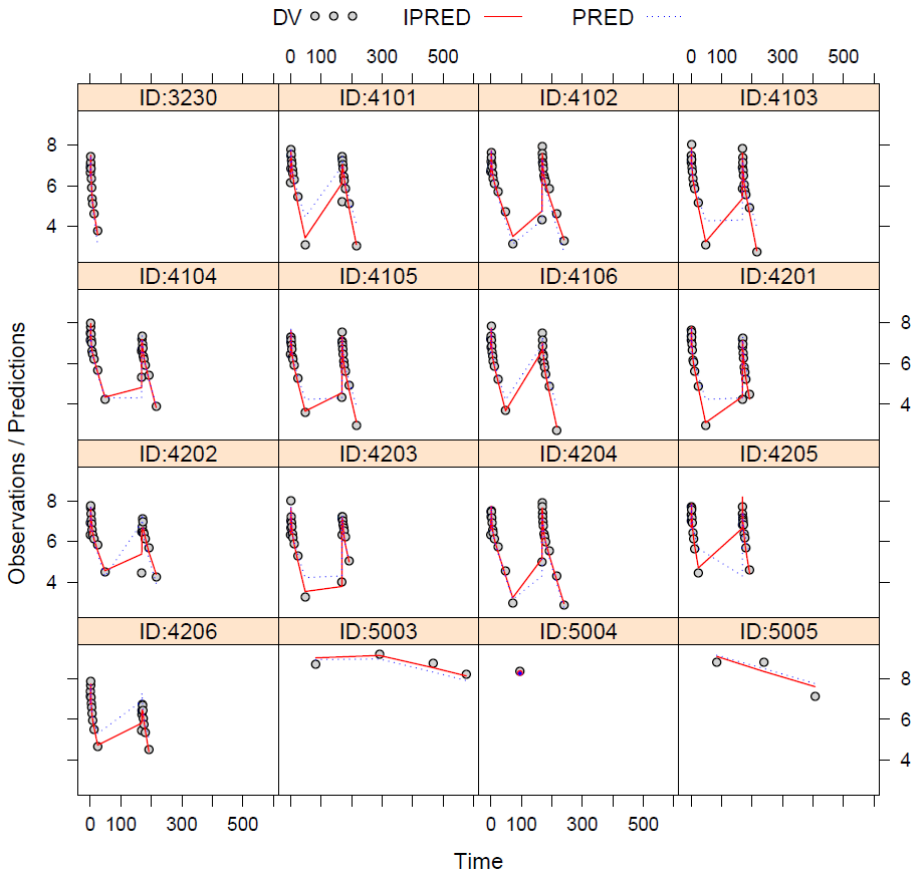
Individual fitting plot for the final pharmacokinetic model (Continued)

Study 1: ID 1001−1111, Study 2: ID 2001−2012, Study 3: ID 3101−3230, Study 4: ID 4101−4206, Study 5: ID 5003−5110



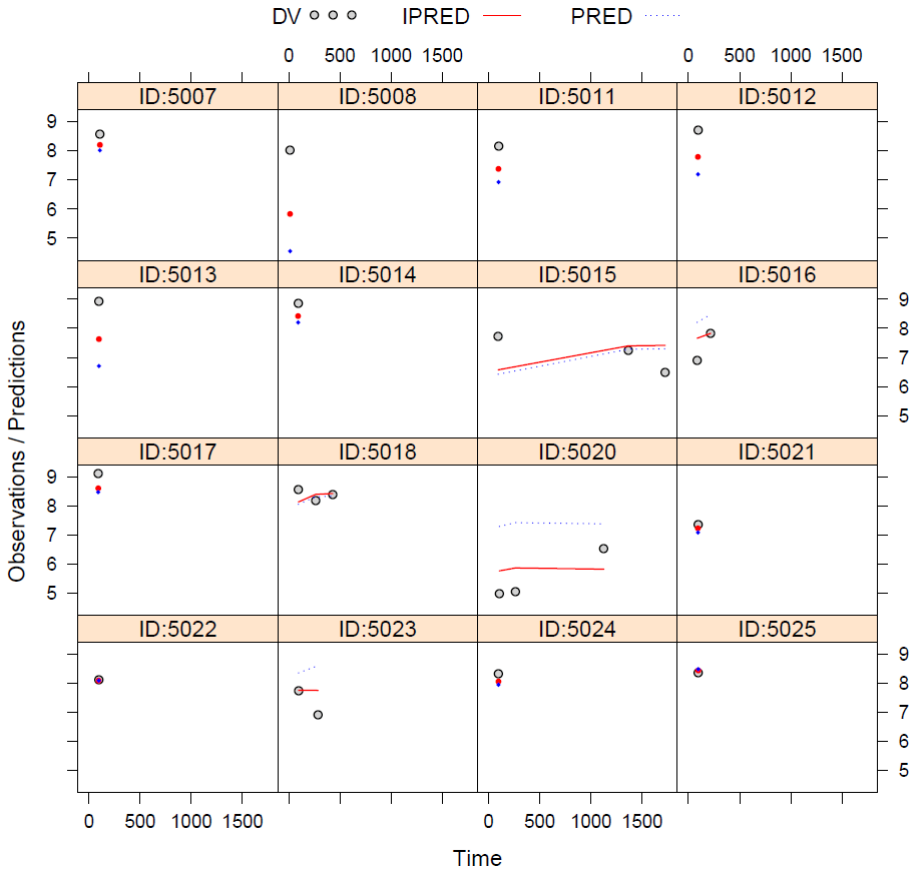
Individual fitting plot for the final pharmacokinetic model (Continued)

Study 1: ID 1001−1111, Study 2: ID 2001−2012, Study 3: ID 3101−3230, Study 4: ID 4101−4206, Study 5: ID 5003−5110



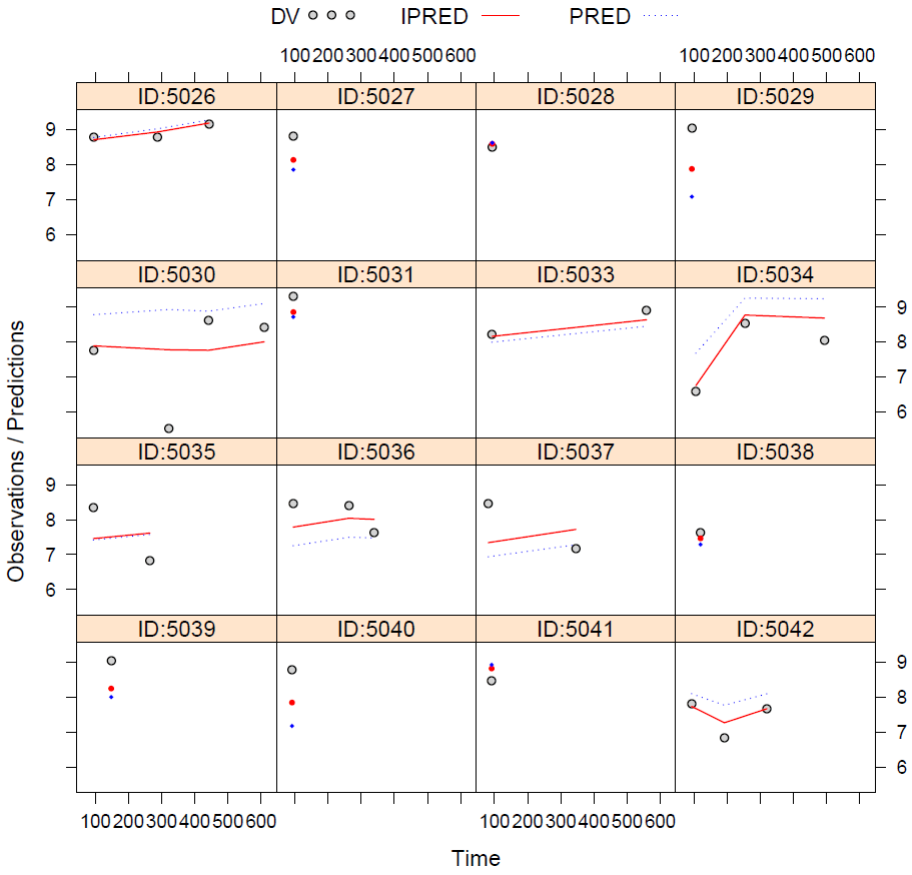
Individual fitting plot for the final pharmacokinetic model (Continued)

Study 1: ID 1001−1111, Study 2: ID 2001−2012, Study 3: ID 3101−3230, Study 4: ID 4101−4206, Study 5: ID 5003−5110



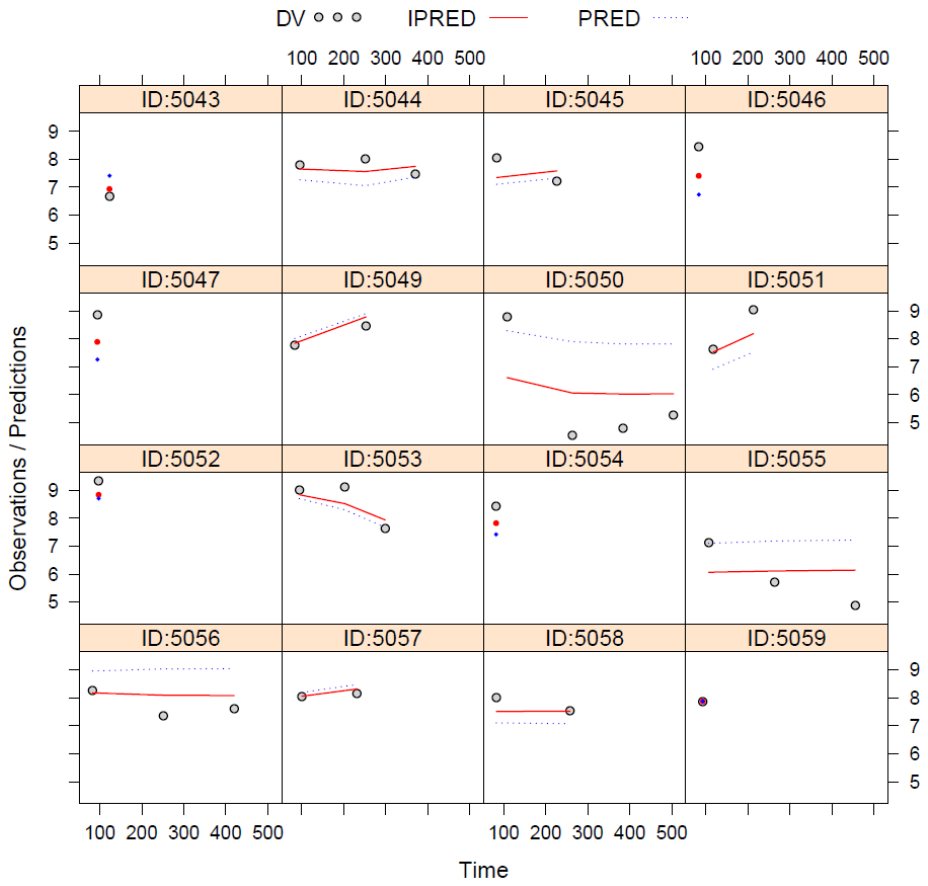
Individual fitting plot for the final pharmacokinetic model (Continued)

Study 1: ID 1001−1111, Study 2: ID 2001−2012, Study 3: ID 3101−3230, Study 4: ID 4101−4206, Study 5: ID 5003−5110



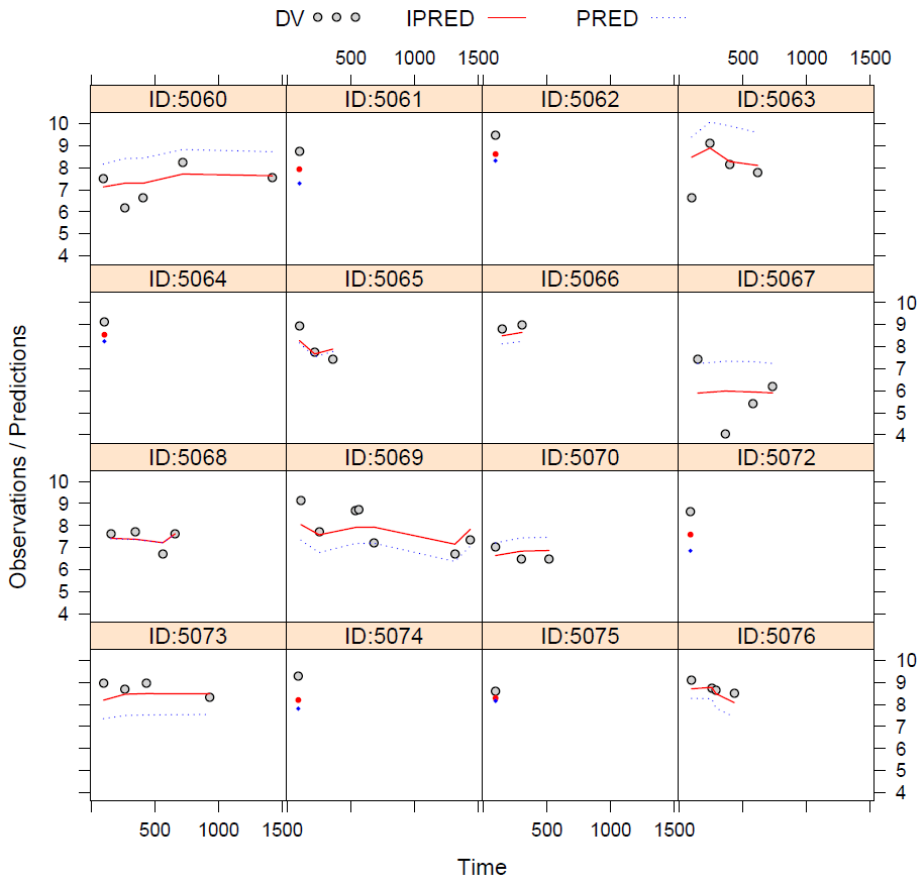
Individual fitting plot for the final pharmacokinetic model (Continued)

Study 1: ID 1001−1111, Study 2: ID 2001−2012, Study 3: ID 3101−3230, Study 4: ID 4101−4206, Study 5: ID 5003−5110



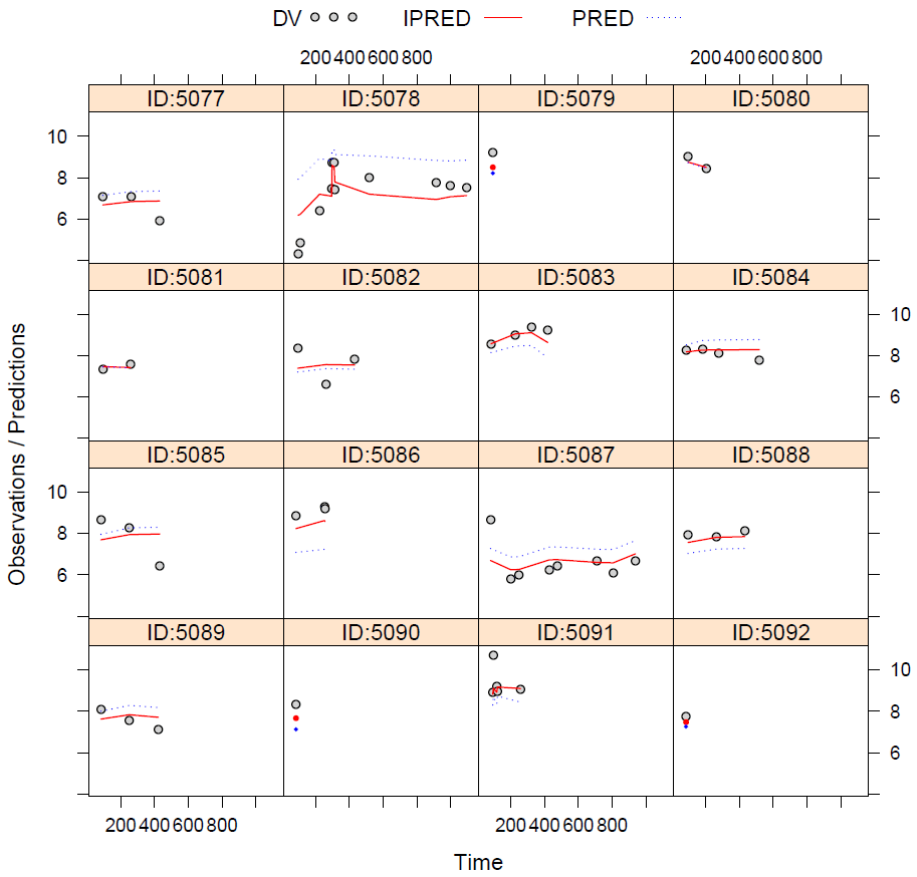
Individual fitting plot for the final pharmacokinetic model (Continued)

Study 1: ID 1001−1111, Study 2: ID 2001−2012, Study 3: ID 3101−3230, Study 4: ID 4101−4206, Study 5: ID 5003−5110



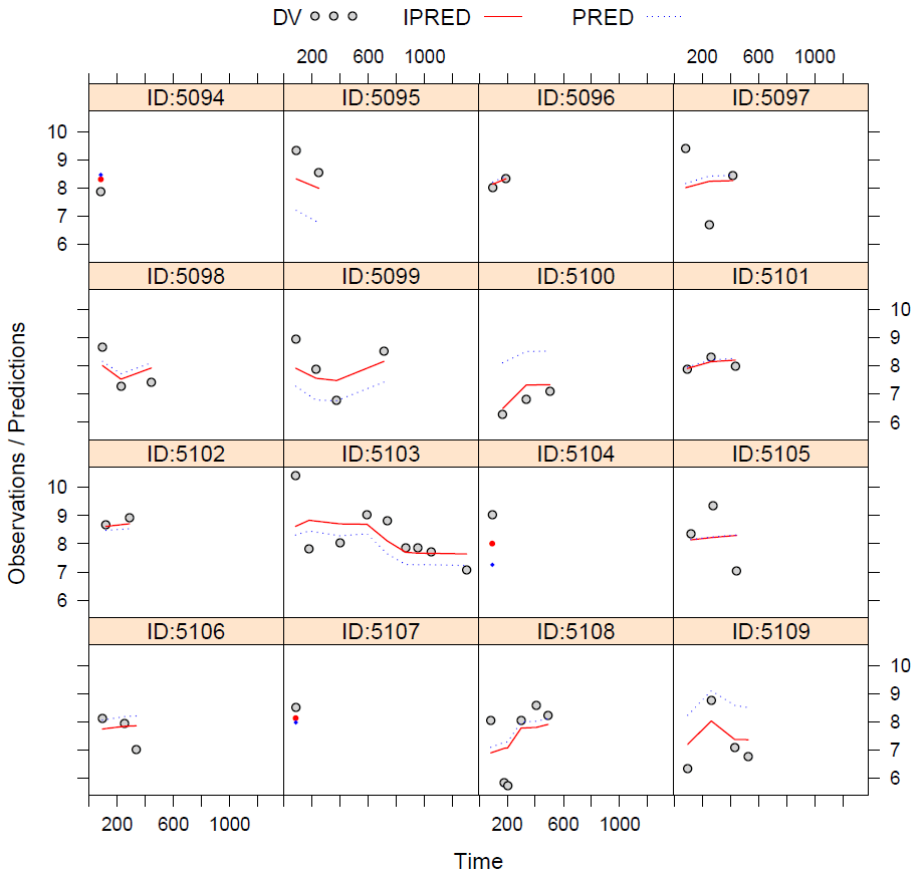
Individual fitting plot for the final pharmacokinetic model (Continued)

Study 1: ID 1001−1111, Study 2: ID 2001−2012, Study 3: ID 3101−3230, Study 4: ID 4101−4206, Study 5: ID 5003−5110



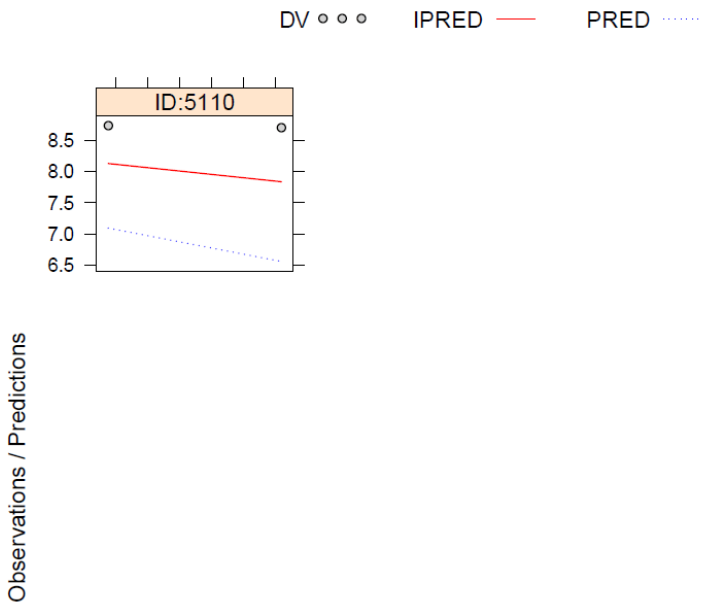
Individual fitting plot for the final pharmacokinetic model (Continued)

Study 1: ID 1001−1111, Study 2: ID 2001−2012, Study 3: ID 3101−3230, Study 4: ID 4101−4206, Study 5: ID 5003−5110



Individual fitting plot for the final pharmacokinetic model (Continued)

Study 1: ID 1001−1111, Study 2: ID 2001−2012, Study 3: ID 3101−3230, Study 4: ID 4101−4206, Study 5: ID 5003−5110



## 2. NONMEM control code for the final pharmacokinetic model

```
$SUBROUTINES ADVAN6 TOL=5

$MODEL
COMP=(DEPOT)
COMP=(CENTRAL)
COMP=(PERIPH1)
COMP=(PERIPH2)
COMP=(INHIBIT)

$PK
;=======================================
IF(GENO.EQ.0) THEN ; RM/EM
GENOF=0
GENOF1=0
ENDIF

IF(GENO.EQ.1) THEN ; IM
GENOF=THETA(17)
GENOF1=THETA(19)
ENDIF

IF(GENO.EQ.2) THEN ; PM
GENOF=THETA(18)
GENOF1=THETA(20)
ENDIF

;=======================================

IF(GRADE.GE.3) THEN ; GRADE 3&4
LFF=THETA(24)
ELSE
LFF=0
ENDIF

;=======================================

TVV2 = THETA(1)
TVCL = THETA(2) * (WT/70)**THETA(16) * EXP(GENOF) *
EXP(LFF)
```

```
TVV3 = THETA(3) * (WT/70)**THETA(15)
TVQ2 = THETA(4) * (WT/70)**THETA(21)
TVV4 = THETA(5)
TVQ3 = THETA(6)

TVKA = THETA(7)
TVF1 = THETA(8)


V2   = TVV2 * EXP(ETA(1))
CL   = TVCL * EXP(ETA(2))
V3   = TVV3 * EXP(ETA(3))
Q2   = TVQ2 * EXP(ETA(4))
V4   = TVV4
Q3   = TVQ3

KA   = TVKA * EXP(ETA(5))
LGF1 = LOG(TVF1/(1-TVF1)) + ETA(6)
F1 = EXP(LGF1) / (1 + EXP(LGF1))

ALAG1 = THETA(9) * EXP(ETA(7))

RCLF = THETA(10) * EXP(GENOF1)* EXP(ETA(8))
IC50 = THETA(11)
KIC = THETA(12)

KE  = CL/V2

K23 = Q2/V2
K32 = Q2/V3

K24 = Q3/V2
K42 = Q3/V4

S2   = V2/1000

$DES
CONC=A(2)/V2
INH= RCLF + (1-RCLF)*(1 - A(5)/(IC50 + A(5)))

DADT(1) = -KA*A(1)
```

```
DADT(2) = KA*A(1) -KE*A(2)*INH - K23*A(2) +
K32*A(3) -K24*A(2) + K42*A(4)
DADT(3) = K23*A(2) - K32*A(3)
DADT(4) = K24*A(2) - K42*A(4)
DADT(5) = KIC*(CONC-A(5))

$ERROR
IPRED=0
IF(F.GT.0) IPRED=LOG(F)

IF(PART.EQ.5) THEN
W = SQRT(THETA(22)**2*IPRED**2 + THETA(23)**2)
ELSE
W = SQRT(THETA(13)**2*IPRED**2 + THETA(14)**2)
ENDIF

Y = IPRED + W*EPS(1)
IRES = DV-IPRED
IWRES = IRES/W

$THETA
(0, 35.6) ; V2
(0, 45.2) ; CL
(0, 56.6) ; V3
(0, 10.3) ; Q2
(0, 25.1) ; V4
(0, 52.6) ; Q3
(0, 1.24) ; KA
(0, 0.859,1) ; F1
(0, 0.235) ; ALAG1
(0, 0.155,1) ;RCLF
(0.01) FIX ; IC50
(0, 0.00234) ;KIC
(0.0001) FIX ; Prop.RE (sd)
(0, 0.31) ; Add.RE (sd)
(0, 2.63) ; WT~V3
(0, 1.11) ; WT~CL
(-0.186) FIX ; IM~CL
(-0.746) FIX ; PM~CL
(-0.51) FIX ; IM~RCLF
(-0.444) FIX ; PM~RCLF
(0, 3.1) ; WT~Q2
```

```
(0.0001) FIX ; Prop.RE (sd) PART5
(0, 0.742) ; Add.RE (sd) PART5
(-0.68) ; GRADE>=3~CL

$OMEGA BLOCK(4)
 0.109   ; IIV V2
 0.0346 0.128   ; IIV CL
 -0.00487 0.019 0.0383   ; IIV V3
 -0.0296 0.0668 0.0147 0.0575   ; IIV Q2
$OMEGA
 0.65 ; IIV KA
 0.179 ; IIV F1
 0 FIX ; IIV ALAG1
 0.4   ; IIV RCLF

$SIGMA
 1 FIX

$EST METHOD=1 INTER MAXEVAL=9999 NOABORT SIG=2
PRINT=1 POSTHOC
$COV

$TABLE ID NTIME TIME NTAD TAD AMT RATE DV MDV
EVID CMT PRD TRT PART IPRED IWRES CWRES
ONEHEADER NOPRINT FILE=sdtab1065
$TABLE V2 CL V3 Q2 KA F1 ALAG1 V4 Q3 RCLF IC50 KIC
ETA1 ETA2 ETA3 ETA4 ETA5 ETA6 ETA7 ETA8
ONEHEADER NOPRINT FILE=patab1065
$TABLE ID AGE WT HT BMI ALP AST ALT GGT CRE GFR
ONEHEADER NOPRINT FILE=cotab1065
$TABLE ID GENO SEX VPC TDM CON PPI USE LFT GRADE
ONEHEADER NOPRINT FILE=catab1065
```

# 국문 초록

**서론**: Voriconazole은 광범위 항진균제로서 invasive aspergillosis의 치료제로 사용되는 약물이다. Voriconazole의 약동학은 CYP2C19 유전형, 인구학적 요소들, 약물 상호작용 및 간기능 등의 여러 요소들로 인해 매우 변동성이 크고 비선형성이 있다고 알려져 있다. 그 중에서도 CYP2C19 유전형이 Voriconazole의 약물노출에 있어 가장 중요한 내인성 요소라고 할 수 있다. 그러나, Voriconazole의 약동학에 CYP2C19 유전형이 미치는 포괄적인 영향은 아직 정량적으로 완벽히 규명되지는 않았다. 그러므로 본 연구에서는 CYP2C19 유전형의 영향을 반영한 Voriconazole의 기전적인 집단 약동학 모델을 개발하고, 이를 활용하여 적절한 치료범위에 근거한 다양한 용량/용법의 적절성을 평가하였다.

**방법**: 본 연구는 Voriconazole을 투여 받은 총 5개의 임상시험 결과를 토대로 건강한 자원자 및 환자의 약동학 자료를 바탕으로 진행되었다. 임상시험에 참여한 대상자들은 Voriconazole을 단회 또는 반복으로 정맥 그리고/또는 경구로 투여 받았다. 본 집단 약동학 분석에 포함된 대상자수는 193명으로 1828개의 농도 자료가 포함되었다. Voriconazole의 약동학에 인구학적 요소, CYP2C19 유전형, 간기능 관련 요소들 및 약물의 병용투여에 대한

영향이 평가되었다. NONMEM을 활용하여 모델 기반 시뮬레이션을 진행하여 치료적 범위에 도달하는 정도를 평가하였다.

**결과**: Voriconazole의 auto-inhibition의 특성을 보이는 약동학적 양상은 억제 구획 모형을 추가한 삼구획 모형으로 적절하게 설명되었다. CYP2C19의 intermediate metabolizer (IM)과 poor metabolizer (PM)의 경우 extensive metabolizer (EM)에 비해 Voriconazole의 청소율이 각각 17%, 53% 감소하였다. CYP2C19 EM 대상자들의 경우 Voriconazole의 청소율이 기존값 대비 16.2%로 억제되는 시간-의존적 양상이 확인되었고, 이러한 양상의 정도는 CYP2C19 유전형에 따라 다르게 나타났다. 간기능이 손상된 환자들의 경우 청소율이 대략 47%정도 감소함이 관찰되었다. 본 연구를 통해 제시한 CYP2C19 유전형에 따른 용량/용법은 EM의 경우 400 mg 하루 두 번, IM의 경우 200 mg 하루 두 번, PM의 경우 100 mg 하루 두 번 투약하는 방법이다.

**결론**: 본 연구는 CYP2C19 유전형과 억제 구획 모형을 활용하여 Voriconazole의 비선형적인 약동학적 양상을 기전적으로 설명하는 첫 번째 시도의 연구 결과이다. 최종적으로 개발된 모델을 토대로 제안한 CYP2C19 유전형에 따른 용량/용법은 향후 치료적 성공을 높일 수 있는 Voriconazole의 개인별 맞춤약물요법으로 활용될 수

있는 근간으로 제시할 수 있다.

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**주요어:** 항진균제; 집단 약동학; 약물유전학; 감염병; 개인별 약물요법

**학 번:** 2017-39391