Impact of CYP2C19 Genotype and Liver Function on Voriconazole Pharmacokinetics in Renal Transplant Recipients

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Background: Invasive fungal infection (IFI) is one of the leading causes of early death after renal transplantation. Voriconazole (VRC) is the first-line drug of IFI. Because of the large inter- and intraindividual variability in VRC plasma concentrations and the narrow therapeutic window for treating patients with IFIs, it is crucial to study the factors which could influence pharmacokinetic variability. We performed a population pharmacokinetics (PPK) study of VRC for personalized medicine.

Methods: A total of 125 trough concentrations (Cmin) from 56 patients were evaluated, retrospectively. Nonlinear mixed effect model was used to describe a PPK model that was internally validated by bootstrap method. Potential covariates included demographic characteristics, physiological and pathological data, concomitant medications, and CYP2C19 genotype.

Results: A 1-compartment model with first-order absorption and elimination was fit to characterize the VRC pharmacokinetics in renal transplant recipients (RTRs). Aspartate aminotransferase (AST) had a significant influence on clearance (CL) while CYP2C19 genotype had a major impact on the volume of distribution (V). The parameters of CL and V were 4.76 L/h and 22.47 L, respectively. The final model was \[ \text{V (L)} = 22.47 \times [1 + 3.30 \times (\text{EM} = 1)] \times [1 + 4.67 \times (\text{IM} = 1)] \times [1 + 3.30 \times (\text{PM} = 1)] \times \exp (0.96); \text{CL (L/h)} = 4.76 \times (\text{AST/33})^{(-0.23)} \times \exp (0.14). \] VRC Cmin in intermediate metabolizers was significantly higher than in extensive metabolizers.

Conclusions: Liver function and CYP2C19 polymorphism are major determinants of VRC pharmacokinetic variability in RTRs. Genotypes and clinical biomarkers can determine the initial scheme. Subsequently, therapeutic drug monitoring can optimize clinical efficacy and minimize toxicity. Hence, this is a feasible way to facilitate personalized medicine in RTRs. In addition, it is the first report about PPK of VRC in RTRs.

Key Words: voriconazole, population pharmacokinetics, renal transplant recipients, CYP2C19 genotype

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INTRODUCTION

Kidney transplantation is the substitutive and lifesaving treatment for some individuals with end-stage renal disease, which can significantly prolong the survival time and improve the quality of life of uremia patients. Clinical studies showed that invasive fungal infection (IFI) is the second leading cause of early death in renal transplant recipients (RTRs), which is a consequence of the long-term use of immunosuppressants and broad-spectrum antibiotics. Despite its low incidence (1.3%), it has a high mortality rate (40%–60%) of IFI, especially in invasive pulmonary aspergillosis (81.3%). It has been reported that patients with IFI have an increased risk of delayed graft function and multiple infections.

Voriconazole (VRC) is an azole compound with a broad-spectrum antifungal activity. Currently, it is the gold standard therapy of invasive aspergillosis, and other serious IFIs. It is recommended that VRC requires for therapy drug monitoring (TDM), due to its wide intra- and interindividual variability, narrow therapeutic range, and risk of toxicity including neurotoxicity (auditory hallucinations...
and hepatic encephalopathy), liver and visual toxicity. As a result, it is important to find crucial factors associated with pharmacokinetic variability of VRC.

To date, published data regarding RTRs taking VRC are limited to epidemiology, risk factors of infection, and effect on immunosuppressants. Research is mainly focused on hematopoietic stem cell transplantation, liver or lung transplantation, and intensive care patients taking VRC. However, the population pharmacokinetics (PPK) of VRC has not been reported in RTRs.

Accordingly, the aims of the current study were (1) to characterize the PPK model of VRC in RTRs and to explore the crucial factors influencing VRC serum concentration, and (2) to study distribution of CYP2C19 genotype in RTRs and its effect on VRC serum concentration.

**MATERIALS AND METHODS**

**Patients and Methods**

**Patients and Data Collection**

All patients with a history of renal transplantation who were admitted to the hospital and received VRC for the prevention or treatment of IFI from September 2015 to June 2016 were eligible for this study. This was a retrospective observational study at the Department of Urological Organ Transplantation of the Second Xiangya Hospital, Central South University. This study was approved by the Ethics Research Committee of the Second Xiangya Hospital, Central South University (yxlb-lys-201501). Exclusion criteria were as follows: (1) age ≥15 years; (2) concomitant medications known to influence VRC pharmacokinetics (eg., rifampin, a strong inducer of CYP2C19); and (3) patients with significant clinical data missing.

Patients’ medical records were reviewed by using a standardized data collection template, including VRC dosing, frequency and duration of use, demographic information (age, sex, and weight), laboratory test results (blood, liver, and kidney function index), time after transplant, and concomitant medications taken during voriconazole therapy [glucocorticoid and proton pump inhibitors (PPI)]. A blood sample is obtained from each patient to determine the VRC Cmin and CYP2C19 gene phenotype (CYP2C19*2, CYP2C19*3, and CYP2C19*17).

**Blood Sampling and Analytical Assays**

The usual dose for VRC is 200 mg b.i.d. as starting dose. The doses were adjusted based on first Cmin. All Cmin were collected 30 minutes before the next dose. The VRC serum concentrations were analyzed by automatic 2-dimensional liquid chromatography (2D-HPLC; Dmitr Instrument Co Ltd, Hunan, China). Two-dimensional separation condition consists of the following: the first-dimensional chromatographic column was FRO C18 (100 × 3.0 mm, 5 μm, ANAX); mobile phase: 20 mmol/L ammonium acetate–acetonitrile = 48:52 (vol/vol); flow rate: 1.0 mL/min. The second-dimensional chromatographic column was ASTON HD C18 (150 × 4.6 mm i.d., 5 μm, ANAX); mobile phase: 40 mmol/L ammonium acetate–acetonitrile = 85:15 (vol/vol); flow rate: 1.2 mL/min; detection wavelength: 273 nm; column temperature: 45°C; sample size: 200 μL. The linearity range was 0.35–11.3 mcg/mL. The intraday and interday precisions were within 1.94%–2.22% and 2.15%–6.78%, separately. The absolute and relative recovery ranged from 88.2% to 93.6% and from 94.2% to 105.3%. The stability of blood sample at room temperature for 8 hours and in −20°C of 3 repeated freeze–thaw cycles were within ±8% and ±10%, respectively.

**DNA Sequencing and CYP2C19 Genetic Polymorphism**

CYP2C19 phenotypic subgroups were classified into 5 categories, namely: (1) ultrarapid metabolizer (UM, CYP2C19*17/*17), (2) rapid metabolizer (CYP2C19*1/*17), (3) extensive metabolizer (EM, CYP2C19*1/*1), (4) intermediate metabolizer (IM, CYP2C19*1/*2, CYP2C19*1/*3, CYP2C19*2/*2, and (5) poor metabolizer (PM, CYP2C19*2/*2, CYP2C19*2/*3, CYP2C19*3/*3). Blood samples (1–3 mL) for genotype detection were obtained from 56 patients. DNA was purified by using the E.Z.N.A SQ Blood DNA Kit II (Omega Bio-Tek, Norcross, GA) method. Genotype test adopted Sanger dideoxy DNA sequencing method by using ABI3730xl-full automatic sequencing instrument (ABI Co) from BoShang Biotechnology Co Ltd in Shanghai.

**Population Pharmacokinetics Analysis**

Nonlinear mixed effect model (NONMEM) was performed by using Phoenix NLME software (Version 1.4, Pharsight, A Certara Company, USA). Extended least square method (FOCE ELS) was adopted in the whole process. Kruskal–Wallis test was used to analyze the correlation of Cmin with dosage form and time after transplant (P < 0.05).

**Structural Model**

Nonlinear mixed-effects model to analyze PPK may offer the possibility of gaining information on pharmacokinetics from relatively sparse data. We use multiple-trough sampling (Cmin) method and NONMEM to estimate interindividual variability in clearance (CL) and volume of distribution (V), by fixing absorption rate constant (Ka). A study showed that a linear elimination model would appropriate to VRC serum concentration compared with other linear models. The 1-compartment model with first-order absorption and elimination was fitted with VRC pharmacokinetic model and the absorption rate was fixed to a value of 1.1 h. Statistical Model

The following exponential models were used to determine the interindividual variability:

Additive exponential model: 

\[ P_{ij} = P_{pop} \times [1 + (P_{ij}/\text{mean}) \times \theta_j] \times \exp(\eta_{ij}) \]

Proportion exponential model: 

\[ P_{pop} \times (P_{ij}/\text{mean})^{\theta_j} \times \exp(\eta_{ij}) \]

Residual variability was tested by comparing 4 models as follows:
Additive error model: \( C_{\text{obs}} = C_{\text{pred}} + e_i \)

Proportional error model: \( C_{\text{obs}} = C_{\text{pred}} \times (1 + e_i) \)

Combined error model: \( C_{\text{obs}} = C_{\text{pred}} \times (1 + e_i) + e \)

Exponential error model: \( C_{\text{obs}} = C_{\text{pred}} \times \exp^{e_i} \)

The following variables were used for all equations: \( P_{ij} \) is the pharmacokinetic parameter of a certain individual, \( P_{\text{pop}} \) is typical values of PPK parameters, \( P_j \) is covariate (influencing factor), \( \theta_i \) is corrected value of covariate, \( n_{ij} \) is individually random variation with a mean of zero and a variance of \( \omega^2 \); \( C_{\text{obs}} \) is observed concentrations, \( C_{\text{pred}} \) is predicted concentrations, and \( e_i \) is random variation with a mean of zero and a variance of \( \sigma^2 \). The Optimal model was determined by considering objective function value (OFV), coefficient of variation, and RetCode value.

### Covariate Model

Firstly, the correlations between pharmacokinetic parameters and covariates were preliminarily inspected by the line graph. Then, covariates were incorporated in the base model, one at a time, using forward addition and backward deletion (stepwise). A significant covariate was retained when the following criteria were met: (1) a decrease in OFV >3.84 \((P < 0.05)\) was included in forward addition, and an increase in OFV >6.63 \((P < 0.01)\) was significant in backward deletion (approximate to \( \chi^2 \) distribution, \( \chi^2_{0.05,1} = 3.84, \chi^2_{0.01,1} = 6.63 \)), (2) clinical plausibility for added variable, and (3) the 95\% confidence interval (CI) for parameter estimates did not include zero.

### Model Selection and Validation

Goodness-of-fit statistics and graphical plots were used to evaluate the adequacy of fitting. Accuracy and stability of prediction of covariate model were validated by bootstrap method. One thousand resamples from the original data were performed. Mean values and 95\% CI of bootstrap parameters were compared with estimates of the final model.

### RESULTS

#### Patient Demographics and Dose Characteristics

A total of 125 Cmin (a median of 2.18, range = 0.16–9.59 mcg/mL) from 56 inpatients were collected. An

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**TABLE 1. Demographic and Clinical Data**

| Parameter                  | Result                  |
|---------------------------|-------------------------|
| VRC Cmin, µg/mL           | 2.63 ± 2.02 (0.16–9.59) |
| Time after renal transplantation | No. patients (%) |
| ≤1 mo                     | 10 (17.9%)              |
| 1–3 mo                    | 15 (26.8%)              |
| 3–6 mo                    | 6 (10.7%)               |
| 6–12 mo                   | 13 (23.2%)              |
| >1 yr                     | 12 (21.4%)              |
| Sex (Male/Female)         | 39/17 (69.6%/30.4%)     |
| Age, yr                   | 40 ± 8 (18–60)          |
| Weight, kg                | 55 ± 10 (33–78)         |
| HGB, g/L                  | 110 ± 27.5 (66–168)     |
| PLT, 10^9/L               | 194 ± 56.4 (60–356)     |
| ALT, U/L                  | 45.7 ± 108.7 (1.9–681.1) |
| AST, U/L                  | 33.0 ± 48.1 (7.9–311.5) |
| ALB, g/L                  | 35 ± 3.5 (26–46)        |
| TBIL, µmol/L              | 8.9 ± 4.2 (2.6–28.2)    |
| DBIL, µmol/L              | 3.8 ± 2.9 (0.3–19.1)    |
| CREA, mmol/L              | 173.1 ± 129.1 (47.5–544.0) |
| CLcr, mL/min              | 51.8 ± 24.7 (11.6–111.6) |
| RM; EM; IM; PM            | 2; 24; 25; 5 (3.6%; 42.9%; 44.6%; 8.9%) |
| PPI (1/0)                 | 26/30 (46.4%/53.6%)     |
| Glucocorticoid (1/0)      | 39/17 (69.6%/30.4%)     |

ALB, albumin; ALT, alanine aminotransferase; CLcr, creatinine clearance rate; CREA, serum creatinine acid; DBIL, direct bilirubin; HGB, hemoglobin; PLT, platelets; TBIL, total bilirubin.
average of 2–3 blood samples were collected from each patient. Patients’ demographics and characteristics are summarized in Table 1. There was still a broad variation in \( C_{\text{min}} \) of VRC under the monitoring. About 72.1% of \( C_{\text{min}} \) values were in therapeutic window (1.0–5.5 mcg/mL), while 20.0% were subtherapeutic and 8.8% were supratherapeutic. Occurrence of IFI was likely in the rst year after transplantation (78.6%), which is a serious threat for successful outcomes following kidney transplantation.

### Population Pharmacokinetic Analysis

A 1-compartment model with rst-order absorption and elimination was suicient to characterize VRC pharmacokinetics. The population-typical values of \( CL \) and \( V \) were 4.76 L/h and 22.47 L, respectively. Interindividual variability was described by the proportion exponential model, and residual variability was described by proportional error model \( \frac{C_{\text{obs}}}{C_{\text{pred}}} = (1 + 0.15) \). As shown in Figure 1, distribution of conditional weighted residuals (CWRES) in histogram and QQ plot indicated that data met normal distribution.

The stepwise screening process is presented in Table 2. From all 12 covariates, only aspartate aminotransferase (AST) and CYP2C19 genotype were found to exert signiicant inluence on PK parameters and were incorporated into parametric equation. Model 1: \( V (L) = 22.47 \times [1 + 2.21 \times (\text{EM} = 1)] \times [1 + 4.67 \times (\text{IM} = 1)] \times [1 + 3.30 \times (\text{PM} = 1)] \times \exp (0.96); CL (L/h) = 4.76 \times \frac{\text{AST}}{33}\times (-0.23) \times \exp (0.14) \)

Furthermore, we analyzed the association between VRC dosage form, time after transplant, CYP2C19 genetic polymorphism, and \( C_{\text{min}} \). RM and PM metabolizers were not statistically analyzed because the sample sizes were only 2 and 5. No signiicant relationship was found between dosage form, time after transplant, and \( C_{\text{min}} \). It appeared that \( C_{\text{min}} \) in RMs is signiicantly lower than in the other 3 genotype subgroups (as shown in Table 3). The differences of VRC \( C_{\text{min}} \) were statistically signiicant between EMs and IMs (\( P < 0.05 \)). Moreover, the allele frequencies of CYP2C19*2, CYP2C19*3, and CYP2C19*17 were 53.2%, 3.2%, and 4.8%, respectively.

### Model Evaluation

The values of \( \omega_V \), \( \omega_{CL} \), and \( \sigma \) in nal model were obviously lower than in the base model, as seen in Table 4. The nal model has lower interindividual and residual variation, indicating that CYP2C19 genotype and AST incorporated in equations had a signiicant effect on VRC pharmacokinetic. The nal model allowed more accurate prediction of \( C_{\text{min}} \). Although the population-predicted concentrations were strongly biased in the base model in scatter

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**TABLE 2. Results of Stepwise Screening of Individual Covariates**

| Parameters and Covariates* | Objective Function Value (OFV) | Variation of OFV (\( \Delta \text{OFV} \)) | \( P \) |
|-----------------------------|-------------------------------|-----------------------------------|-------|
| Forward: \( P < 0.05 \) (3.841) | Base model | 427.058 | — | |
| CL-AST | 409.735 | —7.323 | <0.01 |
| CL-DBIL | 412.827 | —4.231 | <0.05 |
| CL-CYP | 395.265 | —21.793 | <0.0001 |
| V-Glucocorticoid | 412.615 | —4.443 | <0.05 |
| V-PPI | 411.991 | —5.067 | <0.05 |
| V-CYP‡ | 395.265 | —21.793 | <0.0001 |
| CL-AST, V-CYP‡ | 386.594 | —8.671 | <0.01 |
| Backward: \( P < 0.01 \) (6.635) | V-CYP§ | 395.265 | +8.671 | <0.01 |
| CL-AST | 409.735 | +23.142 | <0.0001 |

*Only inluential covariates were listed. A decrease in \( \text{OFV} > 3.84 (P < 0.05) \) was included in forward addition and an increase in \( \text{OFV} > 6.63 (P < 0.01) \) was signiicant in backward deletion (approximate to \( \chi^2 \) distribution, \( \chi_{0.05,1}^2 = 3.84, \chi_{0.01,1}^2 = 6.63 \)).

†The \( \chi^2 \) distribution of CYP: \( \chi_{0.05,1}^2 = 7.82, \chi_{0.01,1}^2 = 11.34, \chi_{0.01,1}^2 = 16.27 \). The largest decrease in \( \text{OFV} \) was chosen as base for the next step.

‡No effect chosen to add when the third covariate was introduced.

§No effect chosen to subtract.

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**TABLE 3. Mean \( C_{\text{min}} \) in Different CYP2C19 Gene Status**

| Gene Status | Gene Polymorphism | \( C_{\text{min}}, \mu\text{g/mL} \) |
|-------------|-----------------|------------------|
| RM (n = 2, 3.6%) | CYP2C19*1/*17 | 0.40 ± 0.14 |
| EM (n = 24, 42.9%) | CYP2C19*1/*1 | 1.76 ± 1.24* |
| IM (n = 25, 44.6%) | CYP2C19*1/*2, *1/*3, *2/*17 | 3.02 ± 2.07* |
| PM (n = 5, 8.9%) | CYP2C19*2/*2 | 4.43 ± 2.46 |

*EM versus IM, wilcoxon rank sum test, \( P = 0.0011, P < 0.01 \).

RM, rapid metabolizer; EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer.

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**TABLE 4. Comparison of Parameters Between the Basic Model and the Final Model**

| Parameter | Base Model | Final Model |
|---------|------------|-------------|
| \( \theta_V \) | Estimate | 95% CI | Estimate | 95% CI |
| \( \theta_{CL} \) | 122.81 | 33.37–212.25 | 22.47 | 10.32–34.61 |
| SD | 5.66 | 4.46–6.68 | 4.76 | 3.52–6.01 |

| \( \omega_V \) | 0.47 | 0.26 | 0.37 | 0.25 |
| \( \omega_{CL} \) | 0.4 | 0.04 | 0.39 | 0.04 |

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plots of detected values versus population-predicted values (Fig. 2A1, B1), the population-predicted concentrations agreed well with the observed voriconazole concentrations in the final model. In addition, CWRES of predicted concentrations of the final model was more uniformly distributed within the range [y = ±2 (±1.96 σ)] (Fig. 2A2, B2). In contrast, the 2 average CWRES trend lines of the base model slightly extended outward at the end. Overall, all of the above illustrates that the final model was more accurate and stable.

Model Validation—Bootstrap Method

Bootstrap is a recommended internal validation method for PPK model based on data resampling technique. All 1000 bootstraps were completed successfully. The population parameter estimates were similar to the simulation values and fell within 95% CI from bootstrap (Table 5). Hence, the model was confirmed to be stable and accurate.

DISCUSSION

Currently, clinicians have increasing interest in prevention and treatment of IFI using VRC. To our knowledge, this is the first PPK study of VRC in RTRs. Recently,17–20 a 1-compartment model was reported to describe the PPK characteristic of VRC in patients. However, there have been conflicting data that support a 2-compartment model with Michaelis clearance.21,22 The inconsistent results may be due to small sample size and limited VRC serum concentration. The V and CL for RTRs were 22.47 L and 4.76 L/h, respectively. By comparison, 2 studies conducted in liver transplant recipients (CL/F = 5.8 ± 5.5 L/h, V_{pcr}/F = 94.5 ± 54.9 L, F = 53%–94%) and lung transplant recipients (CL = 3.45 L/h, Vc = 54.7 L, Vp = 143 L) resulted in a similar CL, although different V was observed.23,24 This difference might attribute to the patients’ underlying disease and immune status.

As shown in Table 2, AST is an indicator for liver function, which significantly affected CL in this study. A
intermediate metabolizers was significantly higher than in extensive metabolizers. This is the first report about PPK of VRC in RTRs.

**TABLE 6.** Comparison of Alleles in Different Populations

| Population  | Sample Size* | 1 (%)† | 2 (%)† | 3 (%)† | 17 (%)† | References            |
|-------------|--------------|--------|--------|--------|---------|------------------------|
| Caucasian   | 111 (35)     | 31     | 20     | None   | 49      | Int J Antimicrob Agents. 2016;47:124–131. |
| Chinese     | 328 (144)    | 41.6   | 50.0   | 6.3    | 2.1     | Int J Antimicrob Agents. 2014;44:436–442. |
| Korean      | 511 (104)    | 61     | 25     | 13     | 1       | Infect Chemother. 2013;45:406–414. |
| Indian      | No data available (55) | 51 | 30 | 0.9 | 18.1 | Int J Clin Pharm. 2015;37:925–930. |
| Thai        | 285 (115)    | 69.6   | 25.6   | 4.8    | None    | Drug Metab Pharmacokinet. 2015;31:117–122. |

*The first number is blood samples, and the value in bracket is the number of patients.
†The allele frequencies of CYP2C19*1, CYP2C19*2, CYP2C19*3 and CYP2C19*17.
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REFERENCES

1. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis. 2010;50:1101–1111.
2. López-Medrano F, Fernández-Ruiz M, Silva JT, et al. Clinical presentation and determinants of mortality of invasive pulmonary aspergillosis in kidney transplant recipients: a multinational cohort study. Am J Transpl. 2016;16:3220–3234.
3. López-Medrano F, Silva JT, Fernández-Ruiz M, et al. Risk factors associated with early invasive pulmonary aspergillosis in kidney transplant recipients: results from a multinational matched case-control study. Am J Transpl. 2016;16:2148–2157.
4. Heylen L, Maetens J, Naesens M, et al. Invasive aspergillosis after kidney transplant: case-control study. Clin Infect Dis. 2015;60:1505–1511.
5. Desbois AC, Poiree S, Snaanoud R, et al. Prognosis of invasive aspergillosis in kidney transplant recipients: a case-control study. Transpl Direct. 2016;2:e90.
6. Patterson TF, Thompson GR, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63:e1–e60.
7. Pappas PG, Kaufman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62:e1–e50.
8. Dolton MJ, McLaIlinan AJ. Voriconazole pharmacokinetics and exposure–response relationships: assessing the links between exposure, efficacy and toxicity. Int J Antimicrob Agents. 2014;44:183–193.
9. Dolton MJ, Ray JE, Chen SC, et al. Multicenter study of VRC pharmacokinetics and therapeutic drug monitoring. Antimicrob Agents Chemother. 2012;56:4793–4799.
10. Racil Z, Wintrove J, Kouha M, et al. Monitoring trough voriconazole plasma concentrations in haematological patients: real life multicentre experience. Mycoses. 2012;55:483–492.
11. Hoyo I, Sanleucente G, de la Bellacasa JP, et al. Epidemiology, clinical characteristics, and outcome of invasive aspergillosis in renal transplant patients. Transpl Infect Dis. 2014;16:951–957.
12. Capone D, Tarantino G, Gentile A, et al. Effects of voriconazole on tacrolimus metabolism in a kidney transplant recipient. J Clin Pharm Ther. 2010;35:125–121.
13. Park SJ, Song IS, Kang SW, et al. Pharmacokinetic effect of voriconazole on cyclosporine in the treatment of aspergillosis after renal transplantation. Clin Nephrol. 2012;78:412–418.
14. Mikus G, Scholz IM, Weiss J. Pharmacogenomics of the triazole antifungal agent voriconazole. Pharmacogenomics. 2011;12:861–872.
15. Beal M, Anuwaa OO, Julia B, et al. Clinical Pharmacogenetics Implementation Consortium (CPCi®) Guideline for CYP2C19 and Voriconazole Therapy. 2016. Available at: https://www.pharmgkb.org/guideline/PA166161537.
16. Guidance for Industry Population Pharmacokinetics. U.S. Department of Health and Human Services Food and Drug Administration. 1999. Available at: http://www.fda.gov/od/center/guidance/index.htm.
17. Farkas A, Daroczi G, Villasurda P, et al. Comparative evaluation of the predictive performance of three different structural population pharmacokinetic models to predict future voriconazole concentrations. Antimicrob Agents Chemother. 2016;60:6806–6812.
18. Pascaul A, Csajka C, Buclin T, et al. Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety: population pharmacokinetics-based analysis of adult patients with invasive fungal infections. Clin Infect Dis. 2012;55:381–390.
19. Wang T, Chen S, Sun J, et al. Identification of factors influencing the pharmacokinetics of voriconazole and the optimization of dosage regimens based on Monte Carlo simulation in patients with invasive fungal infections. J Antimicrob Chemother. 2014;69:463–470.
20. Chen W, Xie H, Liang F, et al. Population pharmacokinetics in China: the dynamics of intravenous voriconazole in critically ill patients with pulmonary disease. Biol Pharm Bull. 2015;38:996–1004.
21. Hope WW. Population pharmacokinetics of voriconazole in adults. Antimicrob Agents Chemother. 2012;56:526–531.
22. Dolton MJ, Mikus G, Weiss J, et al. Understanding variability with voriconazole using a population pharmacokinetic approach: implications for optimal dosing. J Antimicrob Chemother. 2014;69:1633–1641.
23. Johnson HJ, Han K, Capitano B, et al. Voriconazole pharmacokinetics in liver transplant recipients. Antimicrob Agents Chemother. 2010;54:852–859.
24. Han K, Capitano B, Bies R, et al. Bioavailability and population pharmacokinetics of voriconazole in lung transplant recipients. Antimicrob Agents Chemother. 2010;54:4424–4431.
25. Hoening M, Duettmann W, Raggam RB, et al. Potential factors for inadequate voriconazole plasma concentrations in intensive care unit patients and patients with hematological malignancies. Antimicrob Agents Chemother. 2013;57:3262–3267.
26. Lee S, Kim BH, Nam WS, et al. Effect of CYP2C19 polymorphism on the pharmacokinetics of voriconazole after single and multiple doses in healthy volunteers. J Clin Pharmacol. 2012;52:195–203.
27. Wang T, Zhu H, Sun J, et al. Efficacy and safety of voriconazole and CYP2C19 polymorphism for optimised dosage regimens in patients with invasive fungal infections. Int J Antimicrob Agents. 2014;44:436–442.
28. Shimizu T, Ochiiai H, Asell F, et al. Bioinformatics research on interracial difference in drug metabolism I. Analysis on frequencies of mutant alleles and poor metabolizers on CYP2D6 and CYP2C19. Drug Metab Pharmacokinet. 2003;18:48–70.
29. Zonios D, Yamazaki H, Murayama N, et al. Voriconazole metabolism, toxicity, and the effect of cytochrome P450 2C19 genotype. J Infect Dis. 2014;209:1941–1948.
30. Chawla PK, Nanday SR, Dherai AJ, et al. Correlation of CYP2C19 genotype with plasma voriconazole levels: a preliminary retrospective study in Indians. Int J Clin Pharm. 2015;37:925–930.
31. Kim SH, Lee DG, Kwon JC, et al. Clinical impact of cytochrome P450 2C19 genotype on the treatment of invasive aspergillosis under routine therapeutic drug monitoring of voriconazole in a Korean population. Infect Chemother. 2013;45:406–414.
32. Zuo LJ, Guo T, Xia DY, et al. Allele and genotype frequencies of CYP3A4, CYP2C19, and CYP2D6 in Han, Uighur, Hui, and Mongolian Chinese populations. Genet Test Mol Biomarkers. 2012;16:102–108.
33. Chawongwattana S, Jantaraatongtong T, Chitasombat MN, et al. A prospective observational study of CYP2C19 polymorphisms and voriconazole plasma level in adult Thai patients with invasive aspergillosis. Drug Metab Pharmacokinet. 2015;31:117–122.
34. Lamoureux F, Duflot T, Woillard JB, et al. Impact of CYP2C19 genetic polymorphisms on voriconazole dosing and exposure in adult patients with invasive fungal infections. Int J Antimicrob Agents. 2016;47:124–131.