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

Taotao Wang†, Siying Chen†, Jinyue Sun†, Jiangxia Cai†, Xiaoliang Cheng‡, Haiyan Dong†, Xue Wang§, Jianfeng Xing¶, Weihua Dong†, Hongping Yao† and Yalin Dong*†

1Department of Pharmacy, The First Affiliated Hospital of Medical College, Xi’an Jiaotong University, Xi’an 710061, China; 2Department of Pharmaceutics, School of Pharmaceutical Sciences, Peking University Health Science Center, Beijing 100191, China; 3Central Intensive Care Unit, The First Affiliated Hospital of Medical College, Xi’an Jiaotong University, Xi’an 710061, China; 4Department of Pharmacy, College of Medicine, Xi’an Jiaotong University, Xi’an 710061, China

*Corresponding author. Tel: +86-29-85323241; Fax: +86-29-85323240; E-mail: dongyalin@mail.xjtu.edu.cn; dongyalin@medmail.com.cn
†These authors contributed equally to this study.

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Objectives: The objective of this study was to estimate the population pharmacokinetics of voriconazole, to identify the factors influencing voriconazole pharmacokinetics and to identify optimal dosage regimens for attaining target pharmacokinetic/pharmacodynamic indices against Aspergillus and Candida infections in patients with invasive fungal infections (IFIs).

Methods: To prospectively quantify the relationships between the pharmacokinetic parameters of voriconazole and covariates, a population pharmacokinetic analysis was conducted on pooled data from 406 samples taken from 151 patients with IFIs. Voriconazole plasma concentrations were measured by HPLC. The following covariates were tested: demographic factors, laboratory data, concomitant medications and CYP2C19 genotype. Monte Carlo simulation was used to evaluate the effectiveness of the currently recommended dosage regimen and to design an optimized pharmacodynamic dosage strategy for voriconazole.

Results: The data were appropriately fit by a one-compartment model with first-order absorption and elimination. The voriconazole clearance (CL) was 6.95 L/h, the volume of distribution (V) was 200 L and the oral bioavailability (F) was 89.5%. CL was significantly associated with age, the serum concentration of alkaline phosphatase and the CYP2C19 genotype. Based on the results of the Monte Carlo stimulation, we concluded that Aspergillus infections could be treated effectively with 200 mg of voriconazole administered intravenously or orally twice daily and that Candida infections could be treated with 300 mg administered orally twice daily or with 200 mg administered intravenously twice daily.

Conclusions: This study showed that optimal voriconazole dosage regimens could be determined successfully with prospective population pharmacokinetic analyses and Monte Carlo simulations.

Keywords: population pharmacokinetics, pharmacodynamics, NONMEM, Aspergillus, Candida

Introduction

Voriconazole is a new-generation triazole with broad-spectrum antifungal activity against Aspergillus and fluconazole-resistant Candida and Fusarium species, and it is used to treat and prevent invasive fungal infections (IFIs) in clinical practice. A large inter- and intraindividual variability has been observed in the plasma concentrations of voriconazole and concentrations ranging from 0.2 to 12 mg/L have been observed in patients with IFIs treated according to the recommended dosage regimen. Many factors have been found to contribute to this variability, such as polymorphisms of the gene encoding the CYP2C19 enzyme, drug–drug interactions, liver disease and age. The voriconazole plasma concentration is associated with both the efficacy and the adverse effects of the drug, and data obtained from a meta-analysis study suggested a target concentration range of 1–4 mg/L. Because of the large inter- and intraindividual variability in the plasma concentrations of voriconazole and the narrow therapeutic window for treating patients with IFIs, it is necessary to study the population pharmacokinetics of this drug.
In addition, few articles have reported the pharmacokinetic characteristics of voriconazole and population studies are a standard approach for characterizing the determinants of drug pharmacokinetics. The current recommended dosage regimen that was determined in Phase II trials was based on a limited population and the efficacy of voriconazole in patients with IFIs may be different in this limited population than in a broader population. Hence, it is necessary to challenge the recommended dosage regimen to improve efficacy. The Optimizing Pharmacodynamic Target Attainment using the Meropenem Yearly Susceptibility Test Information Collection Antibiogram (OPTAMA) programme utilizes Monte Carlo simulation (MCS) as a tool for determining dosage regimens and assists in the selection of appropriate empirical antibiotic therapies at national, regional and institutional levels. However, no studies have used MCS to identify optimized dosage regimens for voriconazole against *Aspergillus* and *Candida* species.

A pharmacodynamic study of a murine candidiasis model showed that the best predictor of response to voriconazole therapy was free AUC from 0 to 24 h (fAUC₂₄) divided by the MIC (fAUC₂₄/MIC) ≥25. MCS was able to link MIC data with a pharmacokinetic profile to predict the probability of a certain therapeutic outcome, thereby improving antimicrobial effectiveness and the quality of patient care. To estimate the likelihood that voriconazole will effectively treat specific patients, the pharmacokinetic variability must be evaluated in patients, MIC values must be determined in a clinical setting and a pharmacokinetic/pharmacodynamic parameter must be established for clinical efficacy. Together, MCS utilizes the above information to guide the rational design of voriconazole dosage regimens.

In this study, we conducted a population pharmacokinetic analysis with MCS in patients with IFIs receiving voriconazole, with the following aims: (i) to describe the pharmacokinetic characteristics of this drug; (ii) to identify the factors influencing the pharmacokinetic variability of voriconazole; (iii) to evaluate the efficacy of the current voriconazole dosage regimen; and (iv) to establish optimized dosage regimens.

**Patients and methods**

**Patients**

A single-centre clinical trial was conducted from January 2008 to August 2012 at the First Affiliated Hospital of Medical College, Xian Jiaotong University. Patients who were diagnosed with a proven or probable IFI and who were treated with voriconazole were enrolled. IFIs were classified as defined by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group. Patients were selected who received intravenous or oral voriconazole with loading/maintenance doses that were based on the package insert. This study protocol was approved by the institutional review board and included a waiver of informed consent for the anonymous collection and analysis of data. The exclusion criteria were as follows: (i) age < 18 years; (ii) pregnancy; and (iii) lack of compliance with the recommended dosage regimen.

**Data collection**

A number of factors that could potentially influence voriconazole pharmacokinetics were considered, including demographic factors (age and body weight), laboratory data (creatinine clearance rate, platelet count and the levels of serum creatinine, aspartate transaminase, alkaline phosphatase (ALP), alanine aminotransferase (ALT), albumin, total bilirubin (TBIL) and haemoglobin), concomitant medications (CYP2C19 inhibitors, CYP2C19 inducers, CYP3A4 inhibitors and CYP3A4 inducers), CYP2C19 genotype status (ultrarapid metabolizer (CYP2C19*1/*17), extensive metabolizer (CYP2C19*1/*1), intermediate metabolizer (CYP2C19*1/*2 and CYP2C19*1/*3) and poor metabolizer (PM; CYP2C19*2/*2, CYP2C19*2/*3 and CYP2C19*3/*3)) and other factors. Any missing consecutive covariate values were replaced by the corresponding mean values for the population.

**Blood sampling and analytical assays**

Pooled data analysis was performed for the population-based IFIs. In this study, a full pharmacokinetic profile was obtained after intravenous or oral voriconazole for seven patients. The sample times were at 0.5, 1, 1.5, 2, 4, 8, 12, 18 and 24 h after the first dose. Trough samples were collected at interval windows of 10–12 h post-dose. All voriconazole plasma concentrations were measured by HPLC. The lower limit of quantification was 0.06 mg/L. The intraday and interday precisions were within ±6.7% and ±7.6%, respectively. The linearity range was 0.06–8 mg/L (correlation coefficient $R^2 = 0.9998$).

**Population pharmacokinetic analysis**

The concentration–time data were analysed using a non-linear mixed-effects population approach with the NONMEM and subroutine ADIAN6 (version 7.20) software programs to estimate the population value means and the variances of pharmacokinetic parameters, and to identify the factors influencing these parameters.

**Structural model**

The first-order conditional estimation method was applied to all model runs. The search for the best model was performed by comparing one- or two-compartment models with zero- and first-order elimination and Michaelis–Menten elimination after intravenous or oral administration. Different approaches were tested for describing the oral absorption phase including zero- and first-order processes. Because intravenous and oral routes were available in clinical practice, the bioavailability of voriconazole could be characterized in the patients. The typical population values of voriconazole clearance (CL), the volume of distribution (V) and the oral bioavailability (F) were estimated. The absorption rate constant was fixed to a value of 1.1/h, as reported elsewhere.

**Statistical model**

Interindividual variability within the pharmacokinetic parameters was evaluated using exponential error models, each with a mean of 0 and a variance of $a^2$. Various residual variability models were tested, including equations (1–4):

- **Additive error model:** $C_{\text{obs}} = C_{\text{pred}} + \epsilon$ (1)
- **Proportional error model:** $C_{\text{obs}} = C_{\text{pred}} \times (1 + \epsilon)$ (2)
- **Combined error model:** $C_{\text{obs}} = C_{\text{pred}} \times (1 + \epsilon) + \epsilon_1$ (3)
- **Exponential error model:** $C_{\text{obs}} = C_{\text{pred}} \times \exp(\epsilon)$ (4)

In these models, $C_{\text{obs}}$ and $C_{\text{pred}}$ are the observed and predicted concentrations, respectively. $\epsilon$ and $\epsilon_1$ are normal random variables with means of 0 and variances of $a^2$ and $a_1^2$, respectively.
**Covariate model**

All covariates were tested with the basic model and only those covariates that yielded a reduction in the objective function value (OFV) of >3.84 (P<0.05) compared with the basic model were considered to be statistically significant. The influential covariates were then sequentially tested by forward inclusion followed by backward elimination steps to obtain a full model and a final model. A reduction in OFV of >3.84 was considered to be statistically significant for the inclusion of one additional parameter in the forward inclusion steps and an increase in OFV of >10.83 (P<0.001) was considered to be statistically significant in the backward elimination steps. Covariates were included if the following evaluation criteria were met: (i) the OFV was minimized and the precision of the parameter estimates and the goodness of fit (GOF) was improved; (ii) clinical plausibility existed for incorporating the covariates; and (iii) the 95% CIs for the parameter estimates did not include zero.

**Model validation**

The bootstrap method was used to evaluate the robustness of the final model and the precision of the parameter estimations. The results of the bootstrap analyses (mean, 95% CI) were compared with the estimated values of the parameters obtained from the final model. A total of 1000 bootstrap pseudosample evaluations were performed.

**MCS**

This method accounts for the variability in the population pharmacokinetic parameters as well as the MIC data, to determine the probability of reaching a target value of $\frac{AUC_{24}}{MIC} \geq 25$. A value of 58% protein binding in human plasma was employed to simulate $\frac{AUC_{24}}{MIC}$. The estimated mean values and the interindividual variances of the population parameters (CL and F) from the final model were analysed by MCS. The AUC$_{24}$ was then calculated with the following formula:\(^{16}\)

$$AUC_{24} = \text{Dose} \times \frac{F}{\text{CL}}$$

In this equation, Dose is the daily dose, CL is the clearance and F is the oral bioavailability. For intravenously administered voriconazole, F is equal to 1.

Discrete MIC distributions for the Aspergillus and Candida infections were based on the MIC frequencies of the clinical isolates (Figure 1). Simulations were performed for the recommended dosage regimen and for lower and higher dosages, in order to predict the outcomes of various dosage regimens in patients. The MCS was performed with 1000 replicates. The results of the MCS were expressed as the probability of target attainment (PTA) and the cumulative fraction of response (CFR).\(^{17}\) The optimal dosage regimens were evaluated to compare the simulated PTA and CFR in these subjects. A CFR value of ≥90% was considered to be an appropriate empirical dosage regimen, as previously established by the OPTAMA programme.\(^{18}\)

**Results**

**Patient demographics and characteristics**

From January 2008 to August 2012, a total of 406 voriconazole concentrations [a median of 4 per patient (range, 1–9)] were measured by HPLC from 151 hospitalized patients. The demographic and clinical data for the covariates that were assessed are shown in Table 1. For patients, the median sampling time was 9.5 h (range, 0.5–11.5 h) after the preceding dose and the median concentration was 1.66 mg/L (range, 0.1–9.16 mg/L).

**Figure 1.** Voriconazole susceptibility of clinical isolates of Aspergillus and Candida species.

**Population pharmacokinetic analysis**

The population pharmacokinetic analysis was based on 406 voriconazole plasma concentrations from 151 patients. A one-compartment model with first-order absorption and elimination adequately described the data. The other absorption and elimination models did not result in a significant decrease in the OFV and did not improve the GOF. The interindividual and residual variability models were best described by an exponential model and a combined error model, respectively.

When each covariate was tested separately with the basic model, a series of covariates were reserved that resulted in significant reductions in OFV [a change in the OFV (ΔOFV) of >3.84]. These reserved covariates are shown in Table 2. Of these covariates, only age (AGE) had a significant impact on CL and V simultaneously. The separate inclusion of body weight yielded no significant reduction in OFV. These screening results were considered for the construction and selection of a final model.

The forward inclusion model-building step resulted in the full model containing AGE, PM, TBIL and ALP as significant covariates for CL and with AGE as a significant covariate for V. The backward elimination model-building step resulted in a final model containing AGE, PM and ALP as significant covariates for CL and with AGE as a significant covariate for V. None of the selected covariates significantly impacted F in the final model. The OFV decreased by 64.48 for four degrees of freedom (P<0.0001) in the final model compared with the basic model. The population estimates of CL, V and F, and the interindividual and residual variability from the final model and the basic model are listed in Table 3.

One of the criteria used for selecting a model was the GOF of the diagnostic plots. Figure 2 shows the improvement of GOF in the final model compared with the basic model. Although the individual prediction concentrations agreed well with the observed plasma voriconazole concentrations, the population prediction concentrations were strongly biased in the basic model. The scatterplots of the population and the individual prediction concentrations versus the observed concentrations showed less bias, and the individual weighted residuals were distributed in an approximately normal manner, and all values were within the accepted range (−2 – 2) in the final model. In addition, the final model yielded a
A decrease in the OFV was referred to the change in the OFV compared with the basic model. A partial covariate is listed. Some patients were administered omeprazole and dexamethasone simultaneously. Concomitant medication, no. (%) of patients.

Table 2. Results of screening of individual covariates with NONMEM

| Parameter | Significant covariate | ΔOFV | P value
<table>
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<tr>
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<tr>
<td>CL</td>
<td>AGE</td>
<td>-23.27</td>
<td>&lt;0.00001</td>
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<tr>
<td></td>
<td>PM</td>
<td>-12.97</td>
<td>&lt;0.001</td>
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<td></td>
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<td>-6.38</td>
<td>&lt;0.05</td>
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<tr>
<td></td>
<td>ALP</td>
<td>-5.56</td>
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</tr>
<tr>
<td></td>
<td>AZM</td>
<td>-5.35</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>TBIL</td>
<td>-4.35</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>ALB</td>
<td>-4.26</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>V</td>
<td>AGE</td>
<td>-8.12</td>
<td>&lt;0.005</td>
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<tr>
<td></td>
<td>CREA</td>
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</tr>
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<td></td>
<td>CLcr</td>
<td>-5.59</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>F</td>
<td>PM</td>
<td>-4.50</td>
<td>&lt;0.05</td>
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AGE, age; PM, poor metabolizer; UM, ultrarapid metabolizer; ALP, alkaline phosphatase; AZM, azithromycin; TBIL, total bilirubin; ALB, albumin; CREA, serum creatinine acid; CLcr, creatinine clearance rate. A decrease in the OFV was referred to the χ² distribution to assess significance.

Table 1. Demographic and clinical data for 151 patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
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| age (years) | 59 ± 21 (18–99)
| body weight (kg) | 59.1 ± 7.8 (35.0–80.0)
| HGB (g/L) | 99.9 ± 22.4 (52.0–168.0)
| PLT (10⁹/L) | 158.7 ± 113.9 (2.8–641.0)
| AST (U/L) | 42.2 ± 57.8 (6.0–586.0)
| ALP (U/L) | 127.2 ± 75.3 (2.0–693.0)
| ALT (U/L) | 34.6 ± 55.3 (1.0–642.0)
| TBIL (mol/L) | 19.8 ± 41.5 (1.7–521.3)
| ALB (g/L) | 31.1 ± 6.0 (1.3–52.4)
| CREA (mmol/L) | 119.6 ± 95.8 (29.9–729.8)
| CLcr (L/min) | 66.1 ± 38.7 (7.1–242.1)

HGB, haemoglobin; PLT, platelets; AST, aspartate transaminase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; TBIL, total bilirubin; ALB, albumin; CREA, serum creatinine acid; CLcr, creatinine clearance rate; EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer.

Model validation

The accuracy and robustness of the final model were evaluated with a non-parametric bootstrap method. The bootstrap analysis showed that for the final model, 814 out of 1000 runs converged successfully. The point population estimates of all parameters were similar to the mean values obtained from bootstrapping and fell within the 95% CI (Table 3). Thus, the bootstrap method confirmed that the pharmacokinetic parameters were accurate and that the final model was robust.

MCS

Figure 3 shows the PTA percentages for the specific MIC values ranging from 0.0625 to 16 mg/L for each dosage regimen, calculated by the pharmacokinetic/pharmacodynamic index and MCS. For an MIC of 1 mg/L, the PTAs for 200 mg administered twice daily by the intravenous and oral routes were 95.6% and 91.2%, respectively, demonstrating that the dosage regimen is effective for individual patients with a low MIC (<1 mg/L). For higher MICs (≥2 mg/L), the PTAs for the dosage regimen were <90%, suggesting that increased doses are needed for individual patients with higher MIC values.

The CFR is an estimate of the proportion of the population achieving a target fAUC₂₄/MIC value ≥25, calculated by the PTAs and the MIC distribution of the microorganisms. As expected, the CFR improved as the dosage increased. For Aspergillus, a dose of 200 mg twice daily afforded CFR estimates of 95.8% and 94.2% for patients treated intravenously and orally, respectively. For Candida, the optimal dosage regimens were found to be 300 mg administered twice daily orally and 200 mg administered twice daily intravenously, which yielded estimated CFR values of 94.4% and 91.0%, respectively (Table 4).

Discussion

The primary purpose of the present study was to develop a compartmental pharmacokinetic model for determining the optimal voriconazole dosages and to identify the factors influencing the pharmacokinetics of voriconazole in patients with IFIs. We found that a one-compartment model best described the disposition of voriconazole in patients with IFIs. This result is similar to those from studies by Nomura et al.19 and Pascual et al.,15 in which the pharmacokinetics of voriconazole were evaluated in patients with haematological malignancies and IFIs, respectively.

In the forward inclusion model-building step, the inclusion of ALP resulted in a significant reduction in the OFV (ΔOFV = 19.53) and the final model showed that higher ALP values were significantly associated with a reduction in CL. A previous clinical trial in routine therapeutic drug monitoring (TDM) also demonstrated a relationship between ALP values and voriconazole plasma concentrations.10–12 It is not surprising that ALT was not identified in the present study, which was not identical to the previous paediatric study,14 as there were considerable differences between the populations studied, such as the sample sizes, the frequencies of the individual covariate values and the compartment models.
Voriconazole is metabolized by the CYP2C19 isoenzyme as part of the major route of elimination.1,25 The mutant CYP2C19*2 and CYP2C19*3 alleles have been found to occur at greater frequencies in Asians than in Caucasians and have been implicated in slower metabolism.25,26 The effect of these genotypes on the pharmacokinetics of voriconazole is not unexpected. In the current study, CYP2C19 polymorphisms were found to be a major factor contributing to the highly variable pharmacokinetics of voriconazole that may result from potentially higher concentrations of the medication.

The estimated F of voriconazole in the present study was 89.5%, which was similar to previously reported values (74%–91%).32,33 Although no covariates were observed to affect F significantly, this observation may have resulted from the design of the data collection, as the disease state, gastrointestinal function and nutrition are known to be important factors influencing voriconazole absorption.1,34

The final objectives of the present study were to evaluate the probability of dosage regimens achieving the target pharmacokinetic/pharmacodynamic index against Aspergillus and Candida isolates and to estimate the minimum daily voriconazole dose that could increase the probability of effective treatment in patients with IFIs. Because the susceptibility of a pathogen is most often unknown when therapy is initiated in patients with IFIs, MCS is a useful tool for integrating the variability in both drug pharmacokinetics and pathogen susceptibility to identify optimal dosage regimens and to improve empirical therapy. MCS can estimate CFR values and then provide information regarding the appropriate dosage regimens for specific populations of patients. In the present study, MCS was performed with the voriconazole dosage regimens of 200 mg administered intravenously twice daily and 200 mg administered orally twice daily. These regimens achieved CFR values of 91.0% and 86.7%, respectively, in patients with Aspergillus infections; they achieved CFR values of 91.0% and 86.7%, respectively, in patients with Candida infections. These results suggest that the currently recommended dosage regimen is effective for Aspergillus infections and that a higher daily dose than the currently recommended dose is required for treating Candida infections. In clinical practice, fluconazole is the first-line management option for the treatment and prophylaxis of Candida infections, followed by voriconazole treatment if the fluconazole treatment fails. Therefore, the MIC values of voriconazole for treating Candida infections displayed a declined susceptibility that may be caused by cross-resistance.35–37 Thus, the recommended oral dose for voriconazole monotherapy should not be administered empirically for the treatment of Candida infections. The regimen of 200 mg administered orally twice daily yielded a lower CFR value (86.7%) for the treatment of Candida infections in patients. Theoretically, dosages of 300 mg administered twice daily orally or 200 mg administered twice daily intravenously may be sufficient for treating Candida infections, as these reactions may result from potentially higher concentrations of the medication.

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dosages yielded estimated CFR values of 94.4% and 91.0%, respectively.

There are two limitations to the present study. (i) The value of $f_{AUC_{24}}/MIC \geq 25$ used as a predictor of the response to voriconazole therapy was obtained from the results of a murine model. Unfortunately, to our knowledge, no human AUC/MIC data are available for voriconazole in the treatment of IFIs. However, a clinical study conducted by Troke et al. showed that the voriconazole trough plasma concentration/MIC ($C_{\text{trough}}$/MIC) ratio is associated with the higher probability of clinical response. Interestingly, the relationship between $C_{\text{trough}}$/MIC and clinical response is largely concordant with the pharmacokinetic/pharmacodynamic target of

Figure 2. Overview of the GOF plots and their improvements in the basic model (left-hand side) and final model (right-hand side). The diagnostic scatterplots of the voriconazole population pharmacokinetic model from top to bottom are as follows: (a) population prediction concentrations versus observed voriconazole plasma concentrations; (b) individual prediction concentrations versus observed voriconazole plasma concentrations; and (c) individual weighted residuals versus time. The diagonal lines in the upper panels represent lines of unity.
AUC12 value was 1.8-fold higher in subjects receiving 300 mg of voriconazole and its metabolism. A study by Lazarus et al. showed that voriconazole exhibits non-linear pharmacokinetics because of the saturation of its metabolism. (ii) Voriconazole is metabolized extensively by the liver, and this discrepancy may be caused by the lack of intensive sampling. With the consequences of accepting a one-compartment linear model based largely on trough data, a linear proportionality in AUC with dose was assumed in the present study. Thus, the doses (>200 mg administered twice daily) that are required for obtaining appropriate PTA or CFR values may be lower than those calculated by MCS. However, the PTA and CFR values that were calculated by MCS were correct following treatment with a dose of 200 mg administered twice daily either orally or intravenously for the CL was accurate in the final model. Further studies are needed to explore the pharmacokinetic profile of voriconazole in patients with intensive sampling.

In conclusion, the population analysis presented in the present study provides a method for predicting the plasma concentrations in patients for specific doses and suggests that the factors of age, CYP2C19 genotype status and ALP value should be taken into consideration clinically. Routine TDM is needed in the clinic, because a fraction of the variability that exists among the plasma concentrations of voriconazole cannot be explained by the final model presented here. Nevertheless, in the absence of further studies, an accurate and stable population pharmacokinetic model combined with a pharmacokinetic/pharmacodynamic index based on MCS appears to be rational for identifying optimal dosage regimens in IFI patients.

Figure 3. Probability that a pharmacodynamic value \( f_{\text{AUC24}/\text{MIC}} \geq 25 \) is achieved at a specific MIC. Open circles, 100 mg twice daily intravenously; open triangles, 200 mg twice daily intravenously; open squares, 300 mg twice daily intravenously; filled circles, 100 mg twice daily orally; filled triangles, 200 mg twice daily orally; filled squares, 300 mg twice daily orally.

<table>
<thead>
<tr>
<th>Dosage regimen</th>
<th>Aspergillus spp.</th>
<th>Candida spp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg twice daily, intravenously</td>
<td>82.2</td>
<td>75.4</td>
</tr>
<tr>
<td>200 mg twice daily, intravenously</td>
<td>95.8</td>
<td>91.0</td>
</tr>
<tr>
<td>300 mg twice daily, intravenously</td>
<td>98.3</td>
<td>95.6</td>
</tr>
<tr>
<td>100 mg twice daily, orally</td>
<td>76.8</td>
<td>72.1</td>
</tr>
<tr>
<td>200 mg twice daily, orally</td>
<td>94.2</td>
<td>86.7</td>
</tr>
<tr>
<td>300 mg twice daily, orally</td>
<td>97.6</td>
<td>94.4</td>
</tr>
</tbody>
</table>

\( f_{\text{AUC24}/\text{MIC}} \geq 25 \). Therefore, a value of \( f_{\text{AUC24}/\text{MIC}} \geq 25 \) as a clinically determined pharmacokinetic/pharmacodynamic target was acceptable. (ii) Voriconazole is metabolized extensively by the CYP2C19 isoenzyme and some studies have reported that voriconazole exhibits non-linear pharmacokinetics because of the saturation of its metabolism. A study by Lazarus et al. showed that on day 14 after the initiation of voriconazole treatment, the AUC12 value was 1.8-fold higher in subjects receiving 300 mg of voriconazole twice daily than in those receiving 200 mg twice daily. In our study, we did not observe non-linear or multicompartamental behaviour of voriconazole and this discrepancy may be caused by the lack of intensive sampling. With the consequences of accepting a one-compartment linear model based largely on trough data, a linear proportionality in AUC with dose was assumed in the present study. Thus, the doses (>200 mg administered twice daily) that are required for obtaining appropriate PTA or CFR values may be lower than those calculated by MCS. However, the PTA and CFR values that were calculated by MCS were correct.

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References


