Model-based Voriconazole Dose Optimization in Chinese Adult Patients With Hematologic Malignancies

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ABSTRACT

Purpose: The objective of this study was to characterize the population pharmacokinetics of voriconazole and to identify factors that significantly affect pharmacokinetic parameters and to further investigate optimal dosage regimens in Chinese adult patients with hematologic malignancies.

Methods: A prospective population pharmacokinetic analysis was performed on 186 concentration measurements obtained from 41 adult patients with hematologic malignancies. All enrolled patients were treated with voriconazole for diagnosed or suspected invasive fungal diseases. Oral voriconazole was routinely administered at a maintenance dose of 200 mg q12h. Serial blood samples were collected after steady-state of each patient. Monte Carlo simulation was applied to optimize dosage strategies.

Findings: A one-compartment model with first-order absorption and elimination adequately described the data. The typical voriconazole clearance was 4.18 L/h, the volume of distribution was 88.9 L, and the absorption rate constant was 0.729 h^{-1}. Clearance and steady-state exposure (AUC_{0-12}) were found to be significantly associated with age and CYP2C19 phenotype. The average AUC_{0-12} of elderly patients (aged 60−90 years) was 2.1 times higher than that of relative younger patients (aged 18−59 years). The average AUC_{0-12} of poor metabolizers (PMs) was approximately 2.5 and 1.8 times higher than that of extensive and intermediate metabolizers (IMs), respectively. Considering both efficacy and tolerability, dosage regimens of 100 and 50 mg orally administered every 12 hours were recommended for elderly IMs and PMs, respectively.

Implications: A population pharmacokinetic model for voriconazole in Chinese adult patients with hematologic malignancies was successfully developed and could well capture voriconazole's pharmacokinetic characteristics. Age and CYP2C19 phenotype were found to significantly influence voriconazole clearance and should be taken into consideration clinically for dose optimization. The optimal dosage strategies in specific clinical scenarios were proposed in this study based on model simulation. Because of the high incidence of mutant CYP2C19*2 and *3 alleles, genetic testing seems to be necessary for Asian elderly patients when voriconazole treatment is initiated. (*Clin Ther*. 2019;41:1151−1163) © 2019 Published by Elsevier Inc.

Keywords: dose optimization, hematologic malignancies, Monte Carlo simulation, population pharmacokinetics, voriconazole.

INTRODUCTION

Invasive fungal diseases (IFDs) are serious infections mainly caused by *Aspergillus* and *Candida* species, which are characterized by high morbidity and mortality in patients with hematologic malignancies.[1,2] Voriconazole is a broad-spectrum

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triazole antifungal agent used for the treatment of proven and probable IFDs, as well as for prophylaxis of these diseases in high-risk patients with hematologic malignancies.[3] A large inter- and intraindividual variability in the plasma concentrations has been observed in various patients treated with the label-recommended voriconazole dosage regimen.[4–8] Many factors such as genetic polymorphism of the CYP2C19 enzyme and nongenetic factors (age, drug–drug interactions, and liver disease) have been reported to contribute to this variability.[9–11] Moreover, a narrow therapeutic window further complicates the rational use of voriconazole. There are increasing evidences of the association between voriconazole exposure and therapeutic outcomes or occurrence of toxicity.[12,13] Therefore, it is important to optimize voriconazole dose to attain the appropriate exposure. Free AUC (*f*AUC) divided by the MIC (*f*AUC/MIC) >20–25 is usually used as the pharmacokinetic (PK)–pharmacodynamic predictor of response to voriconazole therapy.[14] Trough steady-state plasma concentration has been proved to be associated with voriconazole toxicity.[15]

It has been reported that patients with hematologic malignancies have certain idiosyncrasies that may alter the pharmacokinetics of hydrophilic antimicrobials (e.g., voriconazole).[16,17] For example, hypoalbuminemia and agranulocytosis, which may affect the clearance and distribution of such drugs, are commonly seen in these patients. At present, however, the published PK models on voriconazole mainly focused on patients in the intensive care units and patients who receive a renal or lung transplant. The data in patients with hematologic malignancies are limited, especially in Chinese patients, leading to difficulties in dose decision making for this kind of patients in clinical practice. Therefore, it is necessary to evaluate the population pharmacokinetics of voriconazole and to identify optimal dosage regimens in Chinese adult patients with hematologic malignancies.

In this study, we conducted a population PK analysis in Chinese adult patients with hematologic malignancies receiving oral voriconazole, with the following aims: (1) to describe the PK characteristics of this drug, (2) to identify the factors that significantly influence its PK variability, (3) to evaluate the appropriateness of existing empirical dosage regimen, and (4) to design optimal dosage strategies in specific clinical scenarios based on model simulations.

PATIENTS AND METHODS

Patients

A single center clinical trial was conducted from March 2015 to October 2017 at Peking University Third Hospital. Patients with hematologic malignancies treated with voriconazole for diagnosed or suspected IFDs were enrolled. The exclusion criteria were as follows: (1) age < 18 years, (2) pregnancy, and (3) patients with abnormal liver and kidney function, that is, transaminases (aspartate aminotransferase and/or alanine aminotransferase) >2× upper limit of normal, and/or serum creatinine >120 μmol/L. Oral voriconazole was routinely administered at a maintenance dose of 200 mg q12h. This study was approved by Peking University Third Hospital Ethics Committee, and written informed consent was obtained for each participant.

Data Collection

Demographic data (age, sex, body weight, and body mass index), laboratory test data (platelet count, red blood cell count, white blood cell count, and the levels of alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, total protein, albumin, blood urea nitrogen, serum creatinine, and hemoglobin), and concomitant medications (CYP2C19 inhibitors, CYP2C19 inducers) were collected in this study.

Blood Sampling and Analytical Assay

Serial blood samples (2 mL) were collected within one oral dosing interval after steady-state from each patient. The sampling time was at 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours (each patient had at least 2 samples) after administration of a minimum of 11 oral doses (range from the 11th to 39th dose; median, 18th dose). Voriconazole plasma concentrations were measured with a well-validated HPLC-MS/MS method.[18] The linearity range was 0.05 to 10 mg/L ($R^2 = 0.9995$) and the lower limit of quantitation was 0.05 mg/L. The intraday and interday precisions were within 3.75% and 4.26%, respectively. There was no significant relative matrix effect. Voriconazole was stable in plasma for 24

hours at room temperature, for 45 days at –80ºC, and after three freeze–thaw cycles.

CYP2C19 Genotyping

DNA was purified with the Magen HiPure Blood DNA Mini Kit method. Genotyping for CYP2C19*2, CYP2C19*3, and CYP2C19*17 alleles was performed in all patients with the use of fluorescence in situ hybridization technique with TL998A-full automatic sequencing instrument (Xi'an Tianlong Science and Technology Co Ltd). The metabolic phenotype of each patient was identified as follows: ultrarapid metabolizer (UM) [CYP2C19*17/*17], rapid metabolizer (RM) [CYP2C19*1/*17], extensive metabolizer (EM) [CYP2C19*1/*1], intermediate metabolizer (IM) [CYP2C19*1/*2 and CYP2C19*1/*3], and poor metabolizer (PM) [CYP2C19*2/*2, CYP2C19*2/*3, and CYP2C19*3/*3].[19]

Population PK Model Development

Nonlinear mixed effect modelling software (NONMEM, version 7.3.0; ICON Development Solutions, Ellicott City, MD) was used for data analysis. Model building was assisted by Perl-speaks-NONMEM (PsN, version 4.7.0) and the graphical evaluation with R (version 3.3.3) and Xpose (version 4.5.3).

The first-order conditional estimation method with interaction was applied to all model runs. One- and two-compartment models with first-order oral absorption and linear/saturable elimination were compared to evaluate the best basic structural model. The typical population values of voriconazole clearance (CL/F), the volume of distribution (V/F), and the absorption rate constant (K_a) were estimated.

Interindividual variability in voriconazole PK parameters was described by exponential error models with a mean of zero and a variance of ω^2. Various residual variability models were tested, including additive error model, proportional error model, and combined error model, each with a mean of zero and a variance of σ^2.

Association between covariates and PK parameters were first visually evaluated by plotting empirical Bayes estimates against patient variables. Influential covariates were sequentially tested using forward inclusion, followed by backward elimination procedure to obtain a full model and a final model. Continuous covariates were normalized to the population mean values. A reduction in objective function value (OFV; computed as –2 times the log-likelihood) of >3.84 ($P < 0.05$) was considered to be statistically significant for the inclusion of one additional parameter in the forward inclusion step and an increase in OFV of >6.63 ($P < 0.01$) was considered to be statistically significant in the backward elimination step. Covariates were included if the following criteria were met: (1) the OFV was minimized and the goodness-of-fit (GOF) was improved, (2) clinical plausibility existed for incorporating the covariates, and (3) the 95% CIs for the parameter estimates did not include zero.

The adequacy of fitting was examined by plotting GOF (individual prediction concentrations [IPRED] and population prediction concentrations [PRED] versus observed concentrations, respectively; PRED and time after dose versus conditional weighted residuals, respectively). A 2000-times resampling bootstrap approach was applied to evaluate the robustness of the final model. The results of the bootstrap analysis (median, 95% CI) were compared with the estimated values of the parameters obtained from the final model. Visual predictive check (VPC) was used to assess the predictive performance of the final model (with 1000 simulations).

Monte Carlo Simulation

A 10,000-patients simulation was performed for each subpopulation stratified by age (18–59 years,

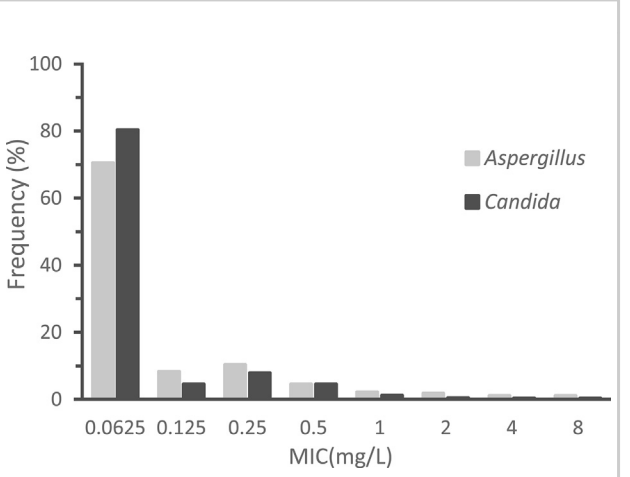

Figure 1. Voriconazole susceptibility of clinical isolates of *Aspergillus* and *Candida* species.

60−90 years) and CYP2C19 phenotype (EM, IM, or PM). The individual steady-state total exposure (AUC_{0-12}) and the steady-state trough concentration ($C_{min,ss}$) were estimated for each subpopulation. To recommend optimal dosing regimens in specific clinical scenarios, various dosing simulations were further performed.

The probability of target attainment (PTA) and the cumulative fraction of response (CFR) were calculated to evaluate the efficacy of each dosage regimen.[20] The probability of reaching a target value of $fAUC_{0-12}$/MIC $\geq$25 was assessed as efficacy index. A value of 58% protein binding in human plasma was adopted to calculate $fAUC_{0-12}$.[11,13] Voriconazole MIC distributions for the *Aspergillus* and *Candida* infections were based on the MIC frequencies of the clinical isolates reported by the clinical microbiology laboratory (Figure 1). The CFR was an estimate of the proportion of the population achieving a target value of $fAUC_{0-12}$/MIC $\geq$ 25, given the PTAs and the MIC distribution of the microorganisms. A CFR value of $\geq$90% was considered to be an appropriate empirical dosage regimen.[13]

The $C_{min,SS}$ distributions of various age/CYP2C19 phenotype combinations receiving either label-recommended or optimized dosage regimens were estimated, based on model simulations. A $C_{min,SS}$ value between 0.5 and 5.0 mg/L was used as a target level according to *Chinese Practice Guideline for Individualized Medication of Voriconazole*.[21]

RESULTS

Patient Characteristics

In this study, a total of 189 voriconazole concentrations (median of 4 per patient; range, 2−9)

Table I. Demographic and clinical characteristics of 41 patients.

Characteristic	Value
Age, mean [SD] (range), y	47 [17] (19−81)
Body weight, mean [SD] (range), kg	62.7 [12.5] (45.0−103.0)
Body mass index, mean [SD] (range), kg/m^2	22.5 [4.0] (14.4−31.8)
Platelets, mean [SD] (range), 10^9/L	164.5 [128.0] (4.0−518.0)
Red blood cells, mean [SD] (range), 10^{12}/L	3.1 [0.7] (2.2−4.4)
White blood cells, mean [SD] (range), 10^9/L	5.5 [2.9] (0.8−13.7)
Alkaline phosphatase, mean [SD] (range), IU/L	77.4 [43.6] (28.0−297.0)
Aspartate aminotransferase, mean [SD] (range), IU/L	28.3 [18.2] (6.0−89.0)
Alanine aminotransferase, mean [SD] (range), IU/L	28.9 [22.0] (6.0−96.0)
Total bilirubin, mean [SD] (range), μmol/L	13.2 [12.2] (0.3−77.0)
Total protein, mean [SD] (range), g/L	61.2 [9.6] (42.0−90.0)
Albumin, mean [SD] (range), g/L	34.2 [6.0] (23.2−45.9)
Blood urea nitrogen, mean [SD] (range), mmol/L	5.9 [2.9] (2.2−14.5)
Serum creatinine, mean [SD] (range), μmol/L	66.6 [17.0] (33.0−107.0)
Hemoglobin, mean [SD] (range), g/L)	92.9 [19.1] (68.0−134.0)
Sex, no.	
Female	18
Male	23
Age $\geq$ 60 years, no.	13
CYP2C19 phenotype, no.	
Extensive metabolizer	18
Intermediate metabolizer	16
Poor metabolizer	7
Concomitant medication, no. (%)	
Esomeprazole	3 (7.3)
Lansoprazole	6 (14.6)

were obtained from 42 patients with hematologic malignancies. All enrolled patients received oral voriconazole at a maintenance dose of 200 mg q12h (ie, median, 6.56 mg/kg/d; range, 3.88–8.89 mg/kg/d), and no dose adjustment based on weight occurred. No UMs were found in these patients. Because only 1 patient belonging to the RM group (with 3 concentration measurements) was observed, the RM group was not investigated in this study. Patient demographic characteristics and corresponding information are summarized in Table I. The median body weight of the patients was 61 kg (range, 45–103 kg). Most of the patients weighed between 50 and 90 kg. There were 4 patients weighing <50 kg and 2 patients weighing >90 kg. Drug was used with caution in this kind of patient and close attention was paid to possible adverse effects. Voriconazole trough concentrations were <0.5 mg/L for 1 patient and >5.0 mg/L for 2 patients. Adverse reactions (visual disturbances and hallucinations) were observed in both patients with trough concentrations >5.0 mg/L.

Model Development

A one-compartment model with first-order absorption and elimination adequately described the data. Either a two-compartment model or a nonlinear Michaelis–Menten elimination model did not result in a significant decrease in OFV and did not describe data better than the linear one-compartment model. The assignment of interindividual variability on *CL/F* and K_a significantly improved the model fit, whereas no variability on *V/F* was observed. The residual variability model was best described by a proportional error model.

The stepwise covariate modelling procedure resulted in the final model that contained age (ΔOFV = –7.204) and CYP2C19 metabolic phenotype (ΔOFV = –9.772) as significant covariates for *CL/F*. In addition, inclusion of allometrically scaled body weight on *CL/F* and *V/F* was found to explain some variability and was kept in the final model. The population estimates of the final model are summarized in Table II.

The typical GOF diagnostic plots are shown in Figure 2. The final model lacked bias regardless of the PRED and time after dose. The PRED and IPRED based on the final model corresponded well with the observed concentrations. The VPC results are shown in Figure 3. The observed median (solid line), observed 5th and 95th percentiles (dashed lines) were adequately within the corresponding simulation-based prediction intervals (shaded areas), suggesting

Table II. Population estimates from the final model[a] and bootstrap analysis results.

Parameters	Values (%RSE)	Bootstrap	
		Median	95% CI
$CL/F_{POP,\ PM}$, L/h	4.18 (9)	4.27	3.15–5.22
α, *the ratio of increase in* CL/F_{POP} *for IM*	0.330 (39)	0.334	0.0389–0.727
β, *the ratio of increase in* CL/F_{POP} *for EM*	0.648 (37)	0.609	0.0982–1.50
V/F_{POP}, L	88.9 (10)	88.1	72.0–111
K_{aPOP}, h^{-1}	0.729 (18)	0.717	0.434–1.26
γ, *age effect on* CL_{POP}	0.0612 (39)	0.0611	0.00264–0.136
IIV_{CL}, %CV	57.7 (25)	54.6	40.6–69.1
IIV_{K_a}, %CV	116 (47)	110	51.5–176
RV, %CV	15.4 (20)	15.2	12.1–18.4

CL/F = apparent elimination clearance; EM = extensive metabolizer; *IIV* = interindividual variability; IM = intermediate metabolizer; K_a = absorption rate constant; PM = poor metabolizer; subscript *POP* = population typical value; *RV* = residual variability; *V/F* = apparent volume of distribution; *WTKG* = body weight (kg); %CV = percent coefficient of variation, calculated as the square root of the variance estimate; %RSE = percent relative standard error of the estimate, calculated as SE/parameter estimate × 100 (for variability terms, this is the %RSE of the variance estimate).

[a] Final model: $CL/F = CL/F_{POP,PM} \times (1+\alpha \times z_1+\beta \times z_2) \times (WTKG/62.7)^{0.75} - (AGE - 47) \times \gamma$, if CYP2C19 phenotype = PM, $z_1 = 0$, $z_2 = 0$; if phenotype = IM, $z_1 = 1$, $z_2 = 0$; if phenotype = EM, $z_1 = 0, z_2 = 1$; $V/F = V/F_{POP} \times (WTKG/62.7)$; $K_a = K_{aPOP}$

acceptable predictive performance of the final model. The bootstrap results for the final model are shown in Table II. All parameter estimates were similar to the median bootstrap values and fell within the 95% CI, indicating the robustness of the final model.

Monte Carlo Simulation

In the context of practical clinical scenario, the steady-state exposure distributions of different subpopulations stratified by either age (Figure 4A) or CYP2C19 phenotype (Figure 4B) are presented. From the developed model in our study, the average AUC_{0-12} of elderly patients was found to be 2.1 times higher than that of younger adult patients, and the average AUC_{0-12} of PMs was approximately 2.5 and 1.8 times higher than that of EMs and IMs, respectively.

Figure 5A shows the PTA percentages at specific MIC values, ranging from 0.0625 to 8 mg/L, for various subpopulations combining age/CYP2C19

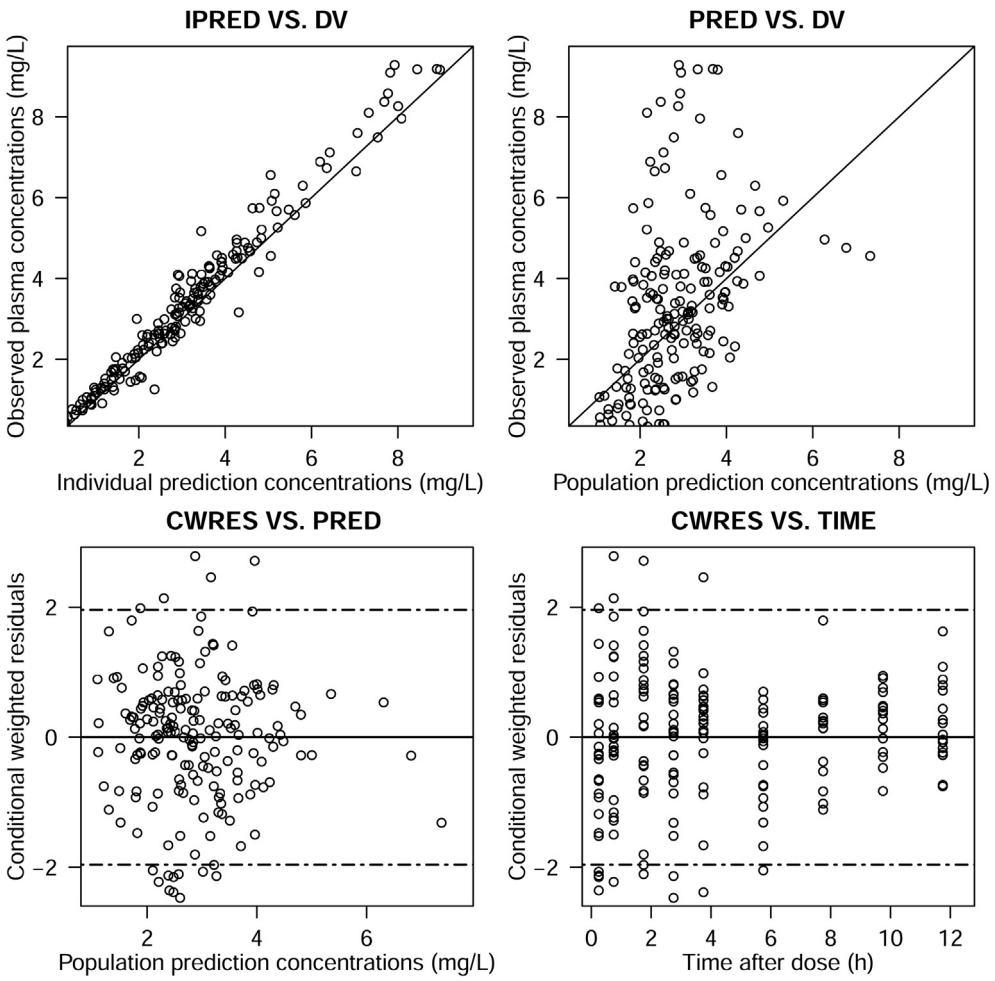

Figure 2. The typical goodness-of-fit diagnostic plots of the final model are as follows: individual prediction concentrations (IPRED) versus observed voriconazole plasma concentrations (DV) (top left), population prediction concentrations (PRED) versus observed voriconazole plasma concentrations (top right), conditional weighted residuals (CWRES) versus population prediction (PRED) concentrations (bottom left), and conditional weighted residuals versus time after dose (TIME) (bottom right). The diagonal lines in the upper panels represent lines of unity.

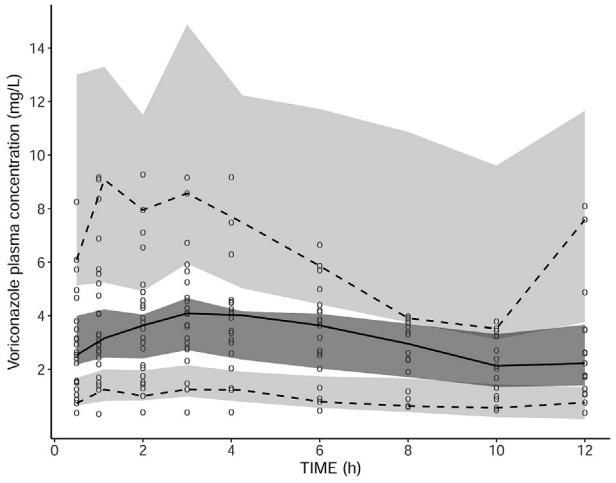

Figure 3. Visual predictive check of the final model. Oral voriconazole was administered at a maintenance dose of 200 mg q12h. The solid line represents the median observed plasma concentration and the semi-transparent black field represents a simulation-based 95% CI for the median. The observed 5% (lower) and 95% (upper) percentiles are presented with dashed lines, and the 95% CIs for the corresponding model predicted percentiles are shown as semi-transparent gray fields. The observed plasma concentrations are represented by black circles.

phenotype. For individual patients with a low MIC (≤0.25 mg/L), oral maintenance dose of 200 mg q12h is adequate. For higher MICs (≥2 mg/L), the PTAs in all subpopulations were <90%, suggesting that the currently recommended empirical dose lacked efficacy. From the PTAs and the MIC distributions of the microorganisms, the existing dosage regimen yielded estimated CFR value of >90% for each specific subpopulation with either *Aspergillus* or *Candida* infections (Table III).

In the case of existing empirical dosage regimen, the $C_{min,SS}$ distributions of various subpopulations combining age/CYP2C19 phenotype are displayed as a violin plot (Figure 6A). Although the $C_{min,SS}$ values of voriconazole varied widely within each subpopulation, most of the $C_{min,SS}$ values of younger adult patients regardless of CYP2C19 phenotype were within an appropriate concentration range (i.e., 89% for EMs, 88% for IMs, and 78% for PMs). However, the proportion of elderly IMs and PMs above toxic concentrations (i.e., 5.0 mg/L) were 35% and 59%, respectively.

Dosage regimens were subsequently simulated in elderly IMs and PMs to attain the appropriate concentration range. Figure 5B shows the PTAs at specific MICs for those patients treated with hypothetical dosage regimens. All the CFR values were estimated to remain >90% as the dosage reduced (Table IV), and when the $C_{min,SS}$ distributions (Figure 6B) were taken into account, 100 and 50 mg orally administered every 12 hours were optimal for elderly IMs and PMs, respectively.

DISCUSSION

In this study, a prospective population PK analysis of voriconazole in Chinese adult patients with hematologic malignancies was successfully performed. A one-compartment model with first-order absorption and elimination best described the data. This result was similar to those from studies by Wang et al,[13] Lin et al,[22] and Pascual et al.[7] The population estimates of *CL/F* and *V/F* in this study were close to the values of critically ill patients reported by Chen et al,[23] but lower than others.[13,22] Although platelet and white blood cell counts were observed to vary widely among patients in this study, neither of them was identified as a significant covariate. Age and CYP2C19 phenotype were found to significantly influence the clearance of voriconazole and should be taken into consideration clinically for dose optimization.

Model results found that the mean voriconazole exposure increased significantly with increasing age. Similar result was reported by Theuretzbacher et al,[11] of which the median voriconazole plasma concentrations were 80% to 90% higher in elderly patients than in younger patients after oral administration with conventional dose. In addition, a direct correlation between age and voriconazole plasma concentration was found in previous clinical trials that involved data from routine therapeutic drug monitoring (TDM).[24,25] Although no dosage

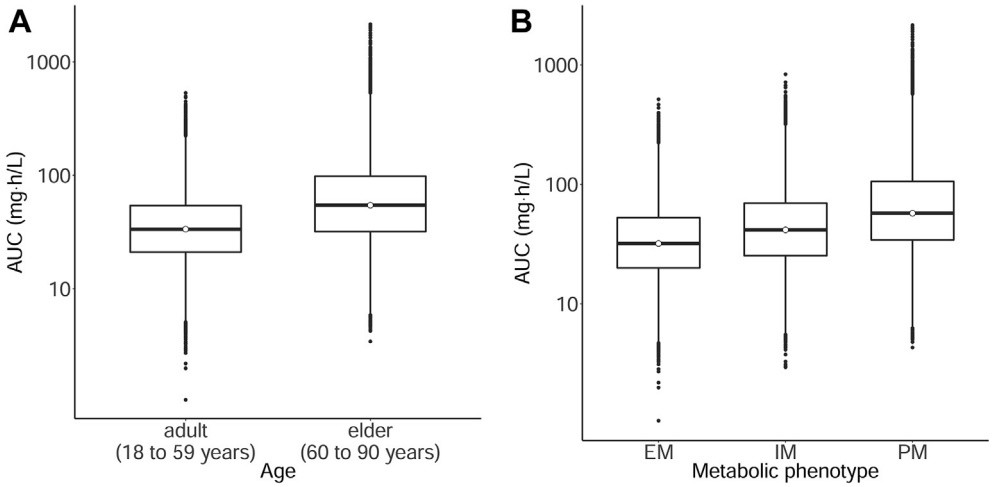

Figure 4. The steady-state exposure distributions of different subpopulations receiving label-recommended dosage regimen stratified by age (A) or CYP2C19 phenotype (B). Each box represents the interquartile distance, with the median indicated by a solid line in the center of the box; the whiskers represent approximately 99% of the data ($\leq$1.5 times the interquartile range), and outliers outside the whiskers are represented by points. EM = extensive metabolizer; IM = intermediate metabolizer; PM = poor metabolizer.

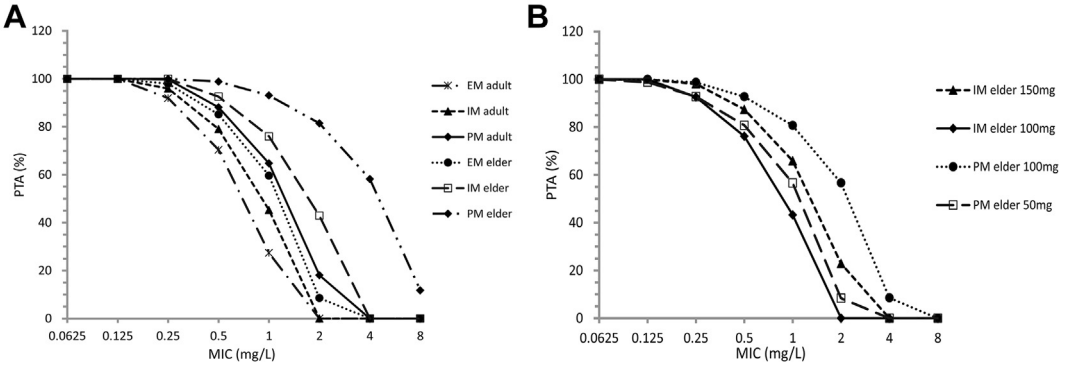

Figure 5. Probability that a target pharmacokinetic–pharmacodynamic parameter value of free AUC_{0-12}/MIC $\geq$ 25 is achieved at a specific MIC for each subpopulation combining age/CYP2C19 phenotype treated with the existing empirical dosage regimen (A) and for elderly intermediate metabolizers (IMs) and poor metabolizers (PMs) treated with hypothetical dosage regimens (B). EM = extensive metabolizer; PTA = probability of target attainment.

adjustment was suggested for the elderly patients according to the product label,[26] the change in voriconazole exposure with age was considered clinically relevant from our simulation results. Therefore, reduced doses were proposed for elderly patients to ensure the tolerability in this study.

CYP2C19 has been proved to be one of the major metabolic pathways of voriconazole

Table III. CFR values for specific subpopulations for treating specific microorganisms with a target value of free AUC_{0-12}/MIC $\geq$25.

Population combination	CFR, %	
	Aspergillus	*Candida*
Younger adult patients (aged 18−59 years)		
EM	92.2	95.8
IM	93.4	96.8
PM	95.0	97.8
Elderly patients (aged 60−90 years)		
EM	94.4	97.4
IM	95.9	98.3
PM	98.0	99.3

CFR = cumulative fraction of response; EM = extensive metabolizer; IM = intermediate metabolizer; PM = poor metabolizer.

elimination.[9,27,28] The mutant CYP2C19*2 and *3 alleles were found to occur at higher frequencies in Asians than in Caucasians, which are associated with slow metabolism of the drug.[29] The incidence of CYP2C19*2 and *3 among East Asians was reported to be 29.0% and 8.3%, respectively, whereas that of CYP2C19*17 was <2%.[22] In contrast, the incidence of CYP2C19*3 in Caucasians was significantly lower (<1%), whereas CYP2C19*17 was 21.3% instead.[22] In our study, the mutant frequencies of CYP2C19*2, *3, and *17 alleles were 32.1%, 4.8%, and 1.2%, respectively, which roughly correspond to the reported data for East Asians. CYP2C19 polymorphism was identified as a significant covariate for *CL/F* in the final model, helping to a large extent explain the highly variable pharmacokinetics of voriconazole. From our developed model, IMs and EMs were found to have approximately one-third and two-thirds higher *CL/F* than their PM counterparts, respectively. Accordingly, dose adjustment was proposed for these kinds of patients and in further should attach importance to Chinese.

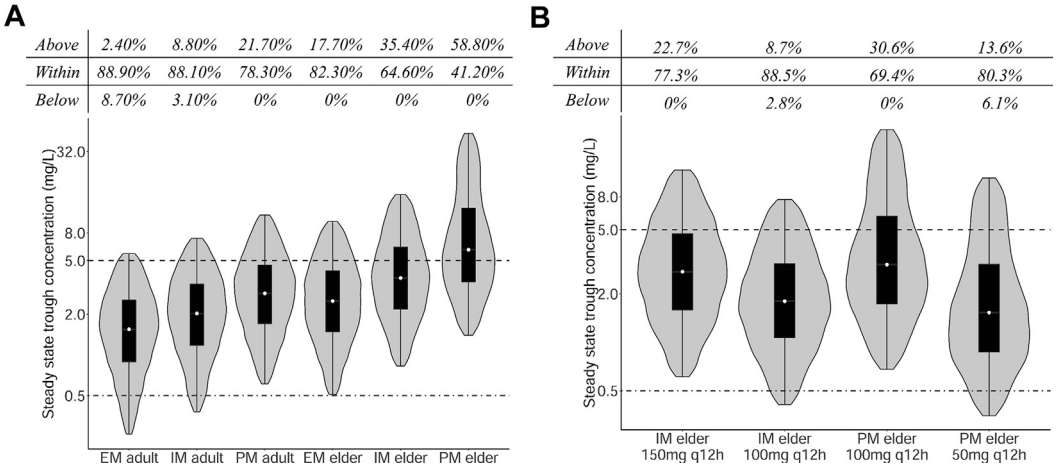

Figure 6. Violin plots of the $C_{min,SS}$ distributions of various subpopulations combining age/CYP2C19 phenotype treated with the existing empirical dosage regimen (A) and $C_{min,SS}$ distributions of elderly intermediate metabolizers (IMs) and poor metabolizers (PMs) treated with hypothetical dosage regimens (B). Each semitransparent gray field represents the probability density distribution of the data from each combination. Each inner black box represents the interquartile distance, with the median indicated by a white solid point in the center of the box; the whiskers represent approximately 99% of the data ($\leq$1.5 times the interquartile range). The dashed lines represent the appropriate concentration range, that is, between 0.5 and 5.0 mg/L. EM = extensive metabolizer.

Table IV. CFR values for specific dosage regimens for treating specific microorganisms with a target value of free AUC_{0-12}/MIC $\geq$25.

Dosage regimen	CFR (%)	
	Aspergillus	*Candida*
Elderly intermediate metabolizers		
150 mg q12h, orally	94.9	97.7
100 mg q12h, orally	92.9	96.3
Elderly poor metabolizers		
100 mg q12h, orally	96.2	98.3
50 mg q12h, orally	93.5	96.7

CFR = cumulative fraction of response.

Coadministration of hepatic microsomal drug-metabolizing enzyme inhibitors or inducers has been reported to some degree to affect the PK parameters of voriconazole.[12,30,31] In this study, esomeprazole and lansoprazole were observed to be the most common concomitant medications that could potentially affect voriconazole pharmacokinetics. However, neither of them was identified as a significant covariate. It has been reported by the US Food and Drugs Administration that the concurrent use of esomeprazole and voriconazole causes no clinically significant change in voriconazole exposure.[32] The study by Qi et al[31] mentioned that esomeprazole had little effect on the metabolic pathway of voriconazole because esomeprazole was metabolized mainly by CYP3A4 but less by CYP2C19. The study also pointed out that lansoprazole did not cause clinically significant inhibition of CYP2C19, which was probably because of its relatively short half-life and high plasma protein binding. Meanwhile, limited data in this study may affect the identification of drug–drug interactions.

CFR values can be estimated so as to integrate the variability in both drug pharmacokinetics and pathogen susceptibility and to provide information about the efficacy of dosage regimens in specific populations. When voriconazole treatment is initiated in patients with hematologic malignancies, the explicit susceptibility of a pathogen is generally unknown. Accordingly, CFR values can be used to identify the most effective dosage regimens and to improve empirical therapy. In this study, both the existing and hypothetical dosage regimens in specific subpopulations with *Aspergillus* or *Candida* infections achieved CFR values of >90%. These findings were attributed in great part to the well-controlled MIC frequencies of the clinical isolates. As shown in Figure 1, a large proportion of the pathogens were distributed at very low MIC level (ie, 0.0625 mg/L).

In this study, $C_{min,SS}$ served as the tolerability indicator for voriconazole. For the existing empirical dosage regimen, most of the $C_{min,SS}$ values from younger adult patients regardless of CYP2C19 phenotype were found to fall within an appropriate concentration range. Therefore, it seemed that no dosage adjustment based on CYP2C19 phenotype was required for such younger patients, although the CYP2C19 phenotype clearly had a significant impact on voriconazole *CL/F*. However, the difference in $C_{min,SS}$ distributions among the elderly patients with different CYP2C19 phenotypes was of a clinically relevant magnitude. Higher concentrations were observed in elderly IMs and PMs, suggesting that a reduced dose of voriconazole should be needed to improve the tolerability. From the simulation results of our study, dosages of 100 and 50 mg orally administered every 12 hours could be sufficient in elderly IMs and PMs, respectively.

Several recent observational studies investigated associations between voriconazole $C_{min,SS}$, toxicity, and efficacy in various Asian patient populations.[33–35] Those studies found that a large inter- and intraindividual variability of voriconazole plasma concentrations was observed in patients who had received a liver transplant (median, 2.49 mg/L; range, 0–11.86 mg/L),[33] patients with hematologic malignancies (median, 2.3 mg/L; range, 0.1–7.1 mg/L),[34] and patients in the intensive care unit (median, 2.6 mg/L; interquartile range, 1.5–4.0 mg/L).[35] Highly variable plasma concentrations (median, 2.23 mg/L; range, 0.38–8.10 mg/L) were also observed in our study, and the extent of variability was comparable with the results of those studies. Therefore, TDM is recommended so as to rapidly identify inappropriate exposure and optimize tolerability and efficacy on an individual basis.

The study by Mangal et al[36] pointed out that the knowledge on the susceptibility of the infecting organism was key for successful antifungal therapy. An *in vitro* study by Siopi et al[37] reported that the susceptible, intermediate, and resistant breakpoints for voriconazole therapy against *A. fumigatus* were set to ≤0.25, 0.5 to 1, and ≥2mg/L, respectively. Similarly, the PTA results obtained from this study suggested that each optimal dosage regimen was effective in patient with a low MIC of ≤0.25 mg/L, considering that a PTA value of >90% was achieved. In contrast, when an MIC was ≥2 mg/L, the PTAs for all specific subpopulations were <50%, suggesting the occurrence of drug resistance. However, increasing the dose could result in high risk of toxicity even though appropriate PTA could be attained in this way. Therefore, it is recommended to choose an alternative or combined antifungal agent rather than to increase the voriconazole dose for patients with high MIC. Isavuconazole, posaconazole, or amphotericin B may be considered as an alternative therapy strategy.[19,38] As indicated in the guidelines, addition of an echinocandin agent to voriconazole is also an attractive option to possibly improve treatment outcomes in select patients with documented invasive aspergillosis.[38] A study by Siopi et al[39] found that the combination of voriconazole with low-dose anidulafungin could increase the efficacy and reduce potential toxicity of antifungal therapy.

The limitations of this study have to be mentioned. Covariate evaluations for some other variables, such as gastrointestinal function and nutrition status which have been reported to influence voriconazole absorption,[11,40] were not supported in this study. In addition, CYP2C19*17 allele was found to be an important determinant of voriconazole exposure.[41] Therefore, studies to quantify the effect of *17 allele carriers are still needed.

CONCLUSION

In summary, the developed model in this study well described the population pharmacokinetics of voriconazole in Chinese adult patients with hematologic malignancies. Age and CYP2C19 phenotype were found to significantly influence voriconazole clearance. Dosage regimens of 100 and 50 mg orally administered every 12 hours were evaluated as suitable empirical dosage regimens for treating elderly IMs and PMs, respectively. Because of the high incidence of mutant CYP2C19*2 and *3 alleles, genetic testing seems to be necessary for Asian elderly patients when voriconazole treatment is initiated. TDM is recommended in consideration of the large inter- and intraindividual variability in voriconazole plasma concentrations. Further studies that involve a large number of patients are needed to confirm the current findings and to clarify their therapeutic implications.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article. The authors have declared that they have no financial and personal relationships with other people or organizations that can inappropriately influence their work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in this article.

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