Population pharmacokinetics, safety and dosing optimization of voriconazole in patients with liver dysfunction: a prospective study

Dan Tang[1], Miao Yan[1], Bai Song[2], Yi-chang Zhao[3], Yi Xiao[4], Feng Wang[4], Wu Liang[5], Bi-kui Zhang[3], Xi Chen[2], Jian Zou[6], Yi Tian[3], Wen-long Wang[3], Yong-fang Jiang[7], guozhong gong[8], Min Zhang[4], and Da-xiong Xiang[3]

[1]the Second Xiangya Hospital of Central South University
[2]China Pharmaceutical University
[3]The Second Xiangya Hospital of Central South University
[4]the Second Xiangya Hospital, Central South University
[5]Changsha VALS Technology Co., Ltd
[6]Nanjing First Hospital, Nanjing Medical University
[7] The Second Xiangya Hospital of Central South University
[8]Second Xiangya Hospital

May 6, 2020

Abstract

Aims This study aimed to explore the relationship between voriconazole trough concentration (Ctrough) and toxicity, identify the factors significantly associated with voriconazole pharmacokinetic parameters and propose an optimised dosing regimen for patients with liver dysfunction. Methods The study prospectively enrolled 51 patients with 272 voriconazole concentrations. Receiver operating characteristic (ROC) curves were used to explore the relationship between voriconazole Ctrough and toxicity. The pharmacokinetic data was analysed with nonlinear mixed-effects method. Dosing simulations stratified by TBIL (TBIL-1: TBIL $<$ 51 μmol/L; TBIL-2: 51 μmol/L [?] TBIL $<$ 171 μmol/L; TBIL-3: TBIL [?] 171 μmol/L) were performed. Results ROC curve analysis revealed that voriconazole Ctrough of [?] 5.1 mg/L were associated with significantly lower the incidence of adverse events. A one-compartment pharmacokinetic model with first-order absorption and elimination was used to describe the data. Population pharmacokinetic parameters of clearance (CL), the volume of distribution (V) and oral bioavailability (F) were 0.88 L/h, 148.8 L and 88.4%, respectively. Voriconazole CL was significantly associated with total bilirubin (TBIL) and platelet count. The V increased with weight. Patients with TBIL-1 could be treated with loading dose of 400 mg every 12 hours (q12h) for first day and maintenance dose of 100 mg q12h intravenously or orally. TBIL-2 and TBIL-3 patients could be treated with loading dose of 200 mg q12h and maintenance doses of 50 mg q12h or 100 mg once daily (qd) and 50 mg qd orally or intravenously, respectively. Conclusions TBIL-based dosing regimens provide a practical strategy for voriconazole maximizing treatment outcomes.

This clinical study was registered in Chinese Clinical Trial Registry (http://www. chictr.org.cn; Registration number: ChiCTR-RRC-1800015015).

Introduction

Infections are common and represent one of the most important reasons of progression of liver failure, development of liver-related complications, and mortality in patients with liver dysfunction [1]. Invasive fungal infections can be a life-threatening complication in patients with liver dysfunction and are associated with a high morbidity and significant mortality [2-5]. Furthermore, long-term use of broad-spectrum antibiotics and glucocorticoids, invasive procedures including liver puncture, ascites drainage, indwelling catheters and hemodialysis, and multiple hospitalizations are also associated with an increased risk of invasive fungal infections [6] and are common in patients with liver dysfunction.

Voriconazole is a triazole antifungal agent that exhibits broad-spectrum activity and is used for both the prevention and treatment of invasive fungal infections [7]. Metabolism of voriconazole occurs in the liver by hepatic cytochrome P450 isoenzymes, primarily CYP2C19 and to a lesser extent CYP3A4 and CYP2C9 [8]. Multiple factors are already known to be associated with variability in voriconazole pharmacokinetics, including age, weight, liver function and genetic polymorphism of the CYP2C19 enzyme [9-12]. Voriconazole exhibits complex nonlinear pharmacokinetics and has a narrow therapeutic window [13, 14]. Subtherapeutic concentrations have been associated with therapeutic failure, and supratherapeutic concentrations are correlated with an increased risk of neurological, visual and hepatic toxicity [14, 15]. Therapeutic drug monitoring (TDM) of voriconazole is advocated to improve treatment outcomes and minimize the risk of adverse events. As the liver plays a key role in the disposition of voriconazole including absorption, distribution, metabolism and excretion [16], liver dysfunction can change the pharmacokinetic characteristics of voriconazole, increasing the risk of voriconazole accumulation and subsequent adverse events.

The voriconazole product information suggests that patients with mild-to-moderate liver dysfunction (Child–Pugh class A and B) should receive half of the maintenance dose after an unchanged loading dose. However, there is limited information about the pharmacokinetics and appropriate dosing of voriconazole in patients with severe liver dysfunction (Child-Pugh class C). We have previously demonstrated that the clearance of voriconazole was significantly decreased in patients with liver dysfunction]17] highlighting the necessity to optimise voriconazole dosing regimens in these patients.

Population pharmacokinetic (PPK) analysis was used to evaluate the pharmacokinetic characteristics and identify the measurable factors of patient-related and clinical-related pharmacokinetic variabilities. Monte Carlo simulation (MCS) is a valuable tool to determine dosing regimens and optimize antibacterial therapies [18]. The present study aims to: 1) develop a PPK model of voriconazole in patients with liver dysfunction; 2) identify factors significantly associated with voriconazole pharmacokinetic parameters; 3) explore the relationship between voriconazole trough concentration (C_{trough}) and toxicity to identify the safety C_{trough} range; 4) evaluate potential voriconazole dosing regimens in patients with liver dysfunction through Monte Carlo Simulation (MCS) utilizing final pharmacokinetic model.

Methods

Patients and Data collection

The prospective and observational study was conducted on liver dysfunction patients who received voriconazole between February 28, 2018 and December 11, 2018. The inclusion criteria were (1) Age[?]15 years; (2) Patients were diagnosed with liver dysfunction, such as liver failure or liver cirrhosis according to the Child-Pugh classifications; (3) Treatment or prevention of invasive fungal infections with voriconazole; (4) patients contributed at least one blood sample. The exclusion criteria were: (1) Patients who were allergic or intolerant to voriconazole; (2) Pregnant or lactating patients; (3) Using potent CYP450 inducer or inhibitor such as rifampicin, isoniazid, phenytoin, carbamazepine during voriconazole treatment, but did not include proton pump inhibitors (PPIs). (4) Patients who lacked the necessary data such as genotype of CYP2C19, renal and liver function index. This study was approved by Ethics Committee of The Second XiangYa

Hospital of Central South University (Changsha, China). All of the patients were provided written informed consent before participating in the study.

Information of the following potential covariates was collected and analyzed: age, gender (Gen), body weight (WT), platelet counts (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), direct bilirubin (DBIL), albumin (ALB), creatinine clearance rate (CLcr) which is calculated using the Cockcroft and Gault equation [19], international normalized ratio (INR), CYP2C19 genotype and concomitant medication (PPIs). Liver dysfunction was classified using Child-Pugh scores [20], and Model for End-stage Liver Disease (MELD) scores. The MELD score according to the following formula [21]:$MELD\ score = 0.957 \times \log_e (creatinine, mg/dl) + 0.378 \times \log_e (bilirubin, mg/dl) + 1.12 \times \log_e (\mathrm{INR}) + 6.43 MELD\ score\ = 0.957 \times \log_e (creatinine, mg/dl) + \log_e (bilirubin,\ mg/dl) + 1.12 \times \log_e (INR)\ + 6.43$

Dosing regimen and Specimen collection

Voriconazole dosing was according to the product information, where patients with mild to moderate liver dysfunction (Child-Pugh A and B) received standard loading doses (400 mg twice daily PO or 6 mg/kg twice daily IV) on the first day, but half the standard maintenance dose (100 mg twice daily PO or 2 mg/kg twice daily IV). Due to the limited data on the dosing of voriconazole in patients with severe liver dysfunction (Child-Pugh C), dosing of these patients was based on the clinician's experience. The subsequent doses for all patients were adjusted according to the measured voriconazole trough concentration (C_{trough}) and the patient's clinical response to voriconazole (effective or ineffective, with or without adverse effects).

Venous blood samples (2 mL) were collected into anticoagulant tubes. Patients were randomly collected 2-3 blood samples without intervention in treatment at 0.5 h, 1 h, 1.5 h, 2 h, 4 h, 6 h, 8 h, 12 h, 24 h after intravenous or oral administration. In addition, blood samples such as C_{trough} from TDM were collected from all patients after 24 hours. All voriconazole plasma concentrations were analysed by automatic two-dimensional liquid chromatography (2D-HPLC, Demeter Instrument Co., Ltd., Hunan, China) as previously described [17].

DNA sequencing and CYP2C19 genetic polymorphism

Genomic DNA was extracted using commercially available EZNA® SQ Blood DNA Kit II. Sanger dideoxy DNA sequencing method with ABI3730xl-full automatic sequencing instrument (ABI Co.) from Boshang Biotechnology Co. Ltd. (Shanghai, China) was used for CYP2C19 genotyping. CYP2C19 phenotypes were classified into five categories: ultrarapid metabolizer (UM, CYP2C19*17/*17), rapid metabolizer (RM, CYP2C19*1/*17), extensive metabolizer (EM, CYP2C19*1/*1), intermediate metabolizer (IM, CYP2C19*1/*2, CYP2C19*1/*3, CYP2C19*2/*17) and poor metabolizer (PM, CYP2C19*2/*2, CYP2C19*2/*3, CYP2C19*3/*3) [22].

Statistical analysis

The Wilcoxon two-sample test or Kruskal–Wallis test was used to compare voriconazole C_{trough}. Proportions were compared with the Chi-square test or Fisher's exact test. Univariate analysis was performed to assess the association between voriconazole C_{trough} and adverse events. Receiver operating characteristic (ROC) curves were used to explore the relationship between voriconazole C_{trough} and adverse events. Statistical analysis was performed with SPSS version 22.0 (IBM Corporation, Armonk, New York).

Population Pharmacokinetics analysis

The concentration–time data of voriconazole was developed using Phoenix NLME (version 8.0, Pharsight Corporation, USA). The first-order conditional estimation method with the η-ε interaction option (FOCE ELS) was used throughout the model development.

One- and two-compartment structural kinetic models with first-order and Michaelis–Menten elimination were evaluated to describe the pharmacokinetics of voriconazole. Finally, we comprehensively compared the objective function value (OFV), graphical goodness of fit, the evaluation of parameter estimates (including precision) and scientific and physiological plausibility to choose the best base model. The oral absorption rate constant (k_a) was fixed to a value of 1.1 h^{-1} based on the results from a previous study [23].

The inter-individual variability in voriconazole pharmacokinetic parameters was described with an exponential error model. Residual error models for voriconazole were tested as follows: the proportional error model, the additive error model and combined error model, including proportional plus additive error model.

Potential demographic and biochemical covariates were evaluated by visual inspection of covariates possible relationships with pharmacokinetic parameters included in the model. For continuous covariates, a linear, piece-wise, exponential, and power parameter-covariate relations were tested. Categorical covariates were linearly included. Then, a covariate model in a stepwise forward-inclusion and backward-elimination procedure were carried out. A covariate was considered to be significant when inclusion of the covariate resulted in a decrease in the objective function value (OFV) of greater than 6.64 ($p< 0.01$) and elimination of the covariate resulted in an increase in the OFV of greater than 10.83 ($p< 0.001$).

Goodness-of-fit (GOF) plots were used to evaluate the adequacy of fitting. The bootstrap method was used to assess the robustness and stability of the final model. 1000 resamples from the original data were performed. All of the model parameters were estimated, and their median and 2.5 and 97.5 percentiles were calculated. That was stable if the 95% CI for the parameter estimates derived from the 1000 bootstrap runs encompassed the original final parameter estimate.

Monte Carlo simulation

1000 individuals receiving the dosing regimens including loading doses of 200, 300 and 400 mg every 12 hours (q12h), and maintenance doses of 50, 100, 150 and 200 mg once daily (qd) or q12h orally or intravenously were simulated by the final model. The dosing regimens were simulated for 30-days and stratified by TBIL (TBIL-1: TBIL $<$ 51 μmol/L; TBIL-2: 51 μmol/L [?] TBIL $<$ 171 μmol/L; TBIL-3: TBIL [?] 171 μmol/L) were performed. The voriconazole C_{trough} range of 0.5-5.0 mg/L [24] was used as the target range. The probability of target attainment (PTA) for the C_{trough} range was examined for each of the different dosing regimens.

Results

Patients' characteristics

51 patients with a total of 272 voriconazole plasma concentrations were included in this study. The demographics and clinical information of the patients is summarized in **Table 1** . Patients with Child-Pugh grade C or MELD score greater than 15 scored made up more than 70% of all patients. There was a significant variation in the voriconazole plasma concentrations, with an average concentration of 3.9 mg/L and a range of 0.06-14.08 mg/L. There were 190 plasma C_{trough}, and 82 plasma concentrations collected within the 24 hours after intravenous or oral administration. There were four types of CYP2C19 genotypes in the present study, 1 UM patients (CYP2C19*17*17), 24 EM patients (CYP2C19*1*1), 21 IM patients (CYP2C19*1*2, CYP2C19*1*3), and 5 PM patients (CYP2C19*2*2, CYP2C19*2*3). The genotypes were divided into three groups (UM/EM, IM and PM) for the purposes of PPK model development.

Voriconazole concentrations and adverse events

Adverse events were reported in 20 patients (39.2%) during voriconazole therapy. These included dizziness, hallucinations and visual disturbance such as altered colour discrimination, blurred vision and photophobia.

The median duration from voriconazole initiation to onset of adverse events was 2 days (range, 1 to 12 days). The median voriconazole concentration at the time of these adverse events was significantly higher than in patients without adverse events (6.5 mg/L versus 2.3 mg/L, P <0.0001). A ROC curve analysis confirmed voriconazole C_{trough} to be a significant predictor of adverse events, with a voriconazole C_{trough} of [?] 5.1 mg/L found to minimize the incidence of adverse events (Figure 1).

Population Pharmacokinetic Analysis

A one-compartment pharmacokinetic model with first-order oral absorption and elimination adequately describe the data. Inter-individual variability of the parameters was best fitted to an exponential equation, and residual error was best characterized by a proportional error model.

The analysis identified the PLT and TBIL as the most significant covariates for CL and WT as a significant covariate for V. The typical value of CL, V and F of voriconazole obtained in the final model are 0.88 L/h, 148.8 L and 88.4%, respectively. The terminal elimination half-life ($t_{1/2}$) was 117.2 h, and the time for voriconazole to reach steady state is about 30 days. The inter-individual variability of CL and V in final model were 18.0% and 12.0%, respectively. Compared to the base model (CL: 68.3%, V: 15.3%), the inter-individual variability of CL and V significantly decreased in the final model. The η of F is fixed as 0 due to the large of shrinkage for F. The final model parameters and the result of bootstrap are summarized in Table 2.

Goodness-of-fit plots from the basic and final models presenting the correlations between population-predicted concentrations and individual-predicted versus observed concentrations of voriconazole are showed in Figure 2**.** The figure shows improvement in the final model fit has been improved compared to the base model. There was no structural bias in the plot of population-predicted and individual-predicted concentrations versus observed concentrations. The conditional weighted residuals (CWRES) of population-predicted concentrations and time for voriconazole are showed in Figure 3**.** The CWRES random distribution was around zero for voriconazole. The distribution was symmetrical distribution and no concentration- or time-related trends were observed for voriconazole. Most of points were within an acceptable range (-2 to 2).

The bootstrap (n=1000) procedure is summarized in Table 2. All 1000 bootstrap runs fit successfully. The parameter estimates of the final model are similar to those of the bootstrap, suggested good robustness and stability of the final model. The parameters of the final model are within the 95% confidence interval (CI) obtained from bootstrap replications, indicating that the estimates for the pharmacokinetic parameters in the final model are accurate and that the model is stable.

Monte Carlo simulation

The elimination of voriconazole is markedly prolonged (typical value of CL: 0.88 L/h) in patients with liver dysfunction, which means it reaches the steady state about 30 days later. Furthermore, fungal infection treatment usually takes one month or more. Therefore, the dosing regimens were simulated at 30-days for treatment. Simulations of oral or intravenous administration did not demonstrated a significant difference. The probability of C_{trough} target attainment after intravenous and oral administration for 30 days of standard unadjusted dosing regimen of voriconazole for patients without liver dysfunction (Loading dose: 400 mg q12h, maintenance dose: 200 mg q12h) are showed in Table 3. The maximum PTA of all group is less than 50%. Apart from TBIL-1 patients, there was 90% overexposure in the other groups. The results for the recommended dosing regimen of voriconazole for patients with mild to moderate liver dysfunction (Child-Pugh A and B) (Loading dose: 400 mg q12h, maintenance dose: 100 mg q12h) are showed in Table 4. The PTA for patients with TBIL-1 is 91.7% and 85.2%, administered orally and intravenously respectively. It indicated that dosing regimen with a loading dose of 400 mg q12h for 2 doses, followed by a maintenance dose of 100 mg q12h administered intravenously or orally for patients with TBIL-1 is suitable.

For patients with TBIL-2 and TBIL-3, we simulated the achievement of C_{trough} after oral and intravenous

administration with different loading doses (400 mg, 300 mg and 200 mg q12h) in order to determine the loading dose, which are showed in Table 5. An oral and intravenous loading dose of 200 mg q12h demonstrated the highest PTA (¿90%). Utilizing this loading dose, different maintenance doses and dosing intervals were simulated to determine the optimal maintenance dose. The PTA of the examined maintenance doses are showed in Table 6. The simulations demonstrated that a maintenance dose of 50 mg q12h or 100 mg qd orally or intravenously for TBIL-2 patients, and a maintenance dose of 50 mg qd orally or intravenously for TBIL-3 patients were optimal. The simulated 30 days median voriconazole C_{trough} versus time profiles based on the optimal intravenous or oral dosing regimen are showed in Figure 4. The results showed that the median voriconazole C_{trough} in all patients were within the target concentration range (0.5-5.0 mg/L), and the distribution of C_{trough} was centralized between 2 and 4 mg/L.

Discussion

This study prospectively investigated 51 patients with liver dysfunction to develop a PPK model. The results of this analysis show that a one-compartment pharmacokinetic model with first-order absorption and elimination was able to describe voriconazole pharmacokinetics in patients with liver dysfunction.

The estimated values of the pharmacokinetic parameters CL, V, and F of voriconazole in patients with liver dysfunction (0.88 L/h, 148.8 L and 88.4%, respectively) are similar to our previous findings [17] (0.56 L/h, 134 L and 80.8%, respectively). We confirmed that voriconazole shows a significant decrease in CL in patients with liver dysfunction compared with patients without liver disease and healthy subjects (CL: 4.76-25.2 L/h) [10, 13, 25, 26]. The V is not significantly different in the presence of liver disease. Covariate model showed that TBIL and PLT are significantly associated with voriconazole CL, while WT has a significant effect on V. The inclusion of TBIL, PLT and WT reduced the inter-individual variation of CL and V (the inter-individual variation of CL decreased from 68.3% to 18.0%, and the inter-individual variation of V decreased from 15.3% to 12.0%), indicating that these covariates are important factors affecting the large variation of pharmacokinetic parameters.

TBIL was showed to be an important covariate affecting the CL of voriconazole in this study, the inclusion of TBIL resulted in a significant reduction of the OFV (ΔOFV=71.36) in the forward inclusion model-building step. The final model demonstrated that high TBIL values were significantly correlated with decreased CL. Voriconazole is mainly metabolized by the CYP450 enzyme in the liver (98%) and then excreted through the kidney and bile, with less than 2% of a dose of voriconazole is excreted into the urine as unchanged voriconazole [27]. In liver disease, a reduction in absolute liver cell mass or a decreased in metabolic enzyme activity may lead to impaired drug metabolism [16], which causes a large amount of voriconazole to accumulate in the body. Therefore, voriconazole CL is significant decrease for patients with liver dysfunction. The PLT was found to be significantly associated with CL in the present study, similar to our previous studies [17]. The reduction of PLT counts is very common in patients with cirrhosis and is correlated with severity of liver function. WT has a significant effect on V, and is positively correlated with V.

Age, CYP2C19 genotype, and PPI were not found to affect significantly the pharmacokinetic parameters of voriconazole, which is consistent with our previous analysis[17]. A prospective study of voriconazole by Wang et al. [28] has shown that age has a significant effect on voriconazole CL, the median voriconazole plasma concentrations in elderly (age [?]65 years) have been 80%-90% higher than those in younger patients. Another prospective study of lung transplant recipients [29] found a correlation between age and initial voriconazole C_{trough}, the older patients (age [?] 60 years) is more likely to have a higher initial C_{trough}. In older patients, the activity of liver microsomal enzyme is decreased, resulting in lower CL. However, this study did not find age to have a significant effect on the pharmacokinetic parameters of voriconazole, suggesting that age has no significant effect on liver microsomal enzymes in patients with liver dysfunction. Many studies [30-33] in patients without liver disease have showed that PM patients have higher voriconazole plasma concentration compared with EM and IM patients. However, CYP2C19 polymorphisms and PPI (CYP2C19

enzyme inhibitors) seem to have no effect on the pharmacokinetic parameters of voriconazole in this study. Ohnishi et al. [34] have reported that in 31 patients with chronic liver disease (9 with chronic hepatitis, 22 with cirrhosis comprising 20 Child-Pugh type A, 1 type B, 1 type C), patients with PM polymorphisms have higher omeprazole hydroxylation indexes (a metabolite of CYP2C19 enzyme) than those with EM and IM polymorphisms, but only two Child-Pugh B and C patients were included. In patients with moderate to severe liver dysfunction, whether gene polymorphism is still an important factor affecting CYP2C19 enzyme activity is worthy of further investigation.

At present, the product information for voriconazole suggests that the standard loading dose should be used but the maintenance dosing should be halved in patients with mild-to-moderate liver disease (Child–Pugh Class A and B), however no dose recommendations in severe liver dysfunction patients are provided. It has been reported in a retrospective study [35] that oral voriconazole maintenance doses in patients with Child–Pugh class C should be reduced to approximately one-third that of patients with normal liver function, while another clinical study for acute-on-chronic liver failure (ACLF) patients [4] has proposed that voriconazole concentration can be maintained a reasonable range (1-5 mg/L) with a loading dose of 200 mg twice daily and a maintenance dose of 100 mg once daily of voriconazole dosing regimen. However, both of these studies are retrospective analyses with small sample sizes (6 cases of cirrhosis C grade and 20 cases of chronic acute liver failure, respectively), so the voriconazole dosing regimen for patients with liver dysfunction still needs further verification.

In the current study, TBIL-based simulations after intravenous and oral voriconazole were performed using voriconazole C_{trough}(0.5-5.0 mg/L) as a target with the combination of MCS to optimize voriconazole dosing regimen. The results show that there is no significant difference in the PTA after voriconazole intravenous and oral administration. The dosing regimen for patients with normal liver function (loading dose: 400 mg q12h; maintenance dose: 200 mg q12h) is probably inappropriate for patients with liver dysfunction, and is associated with a high risk of toxicity (51.6%-97.8% probability of toxicity). Patients with TBIL-1 could be treated with loading dose of 400 mg q12h for 2 doses followed by maintenance dose of 100 mg q12h intravenously or orally which is the dosing regimen of patients with mild-to-moderate liver disease (Child–Pugh Class A and B) in the medication label of voriconazole, but it's not suitable for patients with TBIL-2 and TBIL-3. For patients with TBIL-2 and TBIL-3, the PTA of voriconazole within 30 days is greater than 90% when TBIL-2 and TBIL-3 patients could be treated with maintenance doses of 50 mg q12h or 100mg qd and 50 mg qd orally or intravenous, respectively. Meanwhile, the steady-state time (about 30 days) of voriconazole is markedly prolonged in patients with liver dysfunction, a loading dose of 200 mg q12h orally or intravenously must be given to rapidly achieve the voriconazole target concentration.

This study found that adverse events have generally occurred at higher voriconazole concentrations, and ROC curve analysis revealed a significant association between voriconazole C_{trough} and toxicity, with voriconazole C_{trough} of [?] 5.1 mg/L found to minimize the incidence of adverse events, similar to the studies by Dolton et al [36]. and Troke et al [37].

There are several limitations to the present study. Firstly, this study has a small sample size and it is a single-center study. Secondly, this study did not find the CYP2C19 genotype to have a significant effect on the pharmacokinetic parameters of voriconazole, possibly due to the small number of patients with PM and UM polymorphisms included. Thus, the results need further validation in future clinical studies.

Conclusions

This study suggests that the TBIL, PLT and WT are significantly associated with voriconazole pharmacokinetic parameters. TBIL is a critical factor leading to large pharmacokinetic variation of voriconazole. Using MCS to optimize the dosing regimen in patients with liver dysfunction based on our PPK model and TBIL stratification we demonstrated that lower doses and longer administration intervals should be considered for patients with liver dysfunction. This is helpful for clinicians making decisions about voriconazole dosing

regimens, especially to determine efficient initial dosing strategies and in primary hospitals where TDM is not available.

Funding

This study is supported by the Project of Science and Technology Department of Hunan Province, China (No. 2018SK52501)

Acknowledgements

We acknowledge Xiao-Bin Lin, Zi-Wei Li, Yang Zou, Zhu-Feng Wu, Jia-Min Wu, Xiang-Xin Wu for assistance in DNA extraction and collection of clinical data and blood samples. We also thank Indy Sandaradura from the University of Sydney (Australia) for reviewing the final manuscript.

Conflict of interest

The authors have indicated that they have no conflicts of interest.

Reference

1. Jalan R, Fernandez J, Wiest R, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. J Hepatol 2014; 60:1310-1324.
2. Lin LN, Zhu Y, Che FB, Gu JL, Chen JH. Invasive fungal infections secondary to acute-on-chronic liver failure: a retrospective study. Mycoses 2013; 56:429-433.
3. Chen J, Yang Q, Huang J, Li L. Risk factors for invasive pulmonary aspergillosis and hospital mortality in acute-on-chronic liver failure patients: a retrospective-cohort study. Int J Med Sci 2013; 10:1625-1631.
4. Gao J, Zhang Q, Wu Y, et al. Improving survival of acute-on-chronic liver failure patients complicated with invasive pulmonary aspergillosis. Sci Rep 2018; 8:876.
5. Falcone M, Massetti AP, Russo A, Vullo V, Venditti M. Invasive aspergillosis in patients with liver disease. Med Mycol 2011; 49:406-413.
6. Verma N, Singh S, Taneja S, et al. Invasive fungal infections amongst patients with acute-on-chronic liver failure at high risk for fungal infections. Liver Int 2019; 39:503-513.
7. Pearson MM, Rogers PD, Cleary JD, Chapman SW. Voriconazole: a new triazole antifungal agent. Ann Pharmacother 2003; 37:420-432.
8. Hyland R, Jones BC, Smith DA. Identification of the cytochrome P450 enzymes involved in the N-oxidation of voriconazole. Drug Metab Dispos 2003; 31:540-547.
9. Hoenigl 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.
10. Li ZW, Peng FH, Yan M, et al. Impact of CYP2C19 Genotype and Liver Function on Voriconazole Pharmacokinetics in Renal Transplant Recipients. Ther Drug Monit 2017; 39:422-428.
11. Yan M, Wu ZF, Tang D, et al. The impact of proton pump inhibitors on the pharmacokinetics of voriconazole in vitro and in vivo. Biomed Pharmacother 2018; 108:60-64.
12. Lin XB, Li ZW, Yan M, et al. Population pharmacokinetics of voriconazole and CYP2C19 polymorphisms for optimizing dosing regimens in renal transplant recipients. Br J Clin Pharmacol 2018; 84:1587-1597.

13. Purkins L, Wood N, Ghahramani P, et al. Pharmacokinetics and safety of voriconazole following intravenous- to oral-dose escalation regimens. Antimicrob Agents Chemother 2002; 46:2546-2553.
14. Pascual A, Calandra T, Bolay S, et al. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin Infect Dis 2008; 46:201-211.
15. 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.
16. Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol 2008; 64:1147-1161.
17. Tang D, Song BL, Yan M, et al. Identifying factors affecting the pharmacokinetics of voriconazole in patients with liver dysfunction: A population pharmacokinetic approach. Basic Clin Pharmacol Toxicol 2019; 125:34-43.
18. Trang M, Dudley MN, Bhavnani SM. Use of Monte Carlo simulation and considerations for PK-PD targets to support antibacterial dose selection. Curr Opin Pharmacol 2017; 36:107-113.
19. Pierrat A, Gravier E, Saunders C, et al. Predicting GFR in children and adults: a comparison of the Cockcroft-Gault, Schwartz, and modification of diet in renal disease formulas. Kidney Int 2003; 64:1425-1436.
20. Chang Y, Burckart GJ, Lesko LJ, Dowling TC. Evaluation of hepatic impairment dosing recommendations in FDA-approved product labels. J Clin Pharmacol 2013; 53:962-966.
21. Kamath PS, Kim WR. The model for end-stage liver disease (MELD). Hepatology 2007; 45:797-805.
22. Moriyama B, Obeng AO, Barbarino J, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP2C19 and Voriconazole Therapy. Clin Pharmacol Ther 2017; 102:45-51.
23. Pascual 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.
24. Chen K, Zhang X, Ke X, et al. Individualized Medication of Voriconazole: A Practice Guideline of the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society. Ther Drug Monit 2018; 40:663-674.
25. 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.
26. Scholz I, Oberwittler H, Riedel KD, et al. Pharmacokinetics, metabolism and bioavailability of the triazole antifungal agent voriconazole in relation to CYP2C19 genotype. Br J Clin Pharmacol 2009; 68:906-915.
27. Leveque D, Nivoix Y, Jehl F, Herbrecht R. Clinical pharmacokinetics of voriconazole. Int J Antimicrob Agents 2006; 27:274-284.
28. 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.
29. Mitsani D, Nguyen MH, Shields RK, et al. Prospective, observational study of voriconazole therapeutic drug monitoring among lung transplant recipients receiving prophylaxis: factors impacting levels of and associations between serum troughs, efficacy, and toxicity. Antimicrob Agents Chemother 2012; 56:2371-2377.
30. 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.
31. Li X, Yu C, Wang T, et al. Effect of cytochrome P450 2C19 polymorphisms on the clinical outcomes of voriconazole: a systematic review and meta-analysis. Eur J Clin Pharmacol 2016; 72:1185-1193.
32. Lee S, Kim B-H, Nam W-S, et al. Effect of CYP2C19 Polymorphism on the Pharmacokinetics of Voriconazole After Single and Multiple Doses in Healthy Volunteers. The Journal of Clinical Pharmacology 2012; 52:195-203.
33. Weiss J, Ten Hoevel MM, Burhenne J, et al. CYP2C19 genotype is a major factor contributing to the

highly variable pharmacokinetics of voriconazole. J Clin Pharmacol 2009; 49:196-204.
34. Ohnishi A, Murakami S, Akizuki S, et al. In vivo metabolic activity of CYP2C19 and CYP3A in relation to CYP2C19 genetic polymorphism in chronic liver disease. J Clin Pharmacol 2005; 45:1221-1229.
35. Yamada T, Imai S, Koshizuka Y, et al. Necessity for a Significant Maintenance Dosage Reduction of Voriconazole in Patients with Severe Liver Cirrhosis (Child-Pugh Class C). Biol Pharm Bull 2018; 41:1112-1118.
36. Dolton MJ, Ray JE, Chen SC, et al. Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring. Antimicrob Agents Chemother 2012; 56:4793-4799.
37. Troke PF, Hockey HP, Hope WW. Observational study of the clinical efficacy of voriconazole and its relationship to plasma concentrations in patients. Antimicrob Agents Chemother 2011; 55:4782-4788.

Tables

Table . Demographics and clinical information of the study patients (n = 51)

Characteristic	**Value** [a]
Gender (male/female), n	43/8
AGE (years)	46.4±12.8 (47,15-89)
Weight (kg)	60.0 ±13.1 (58,36-99)
PLT count (10^9/L)	85.4±70.8 (65,20-450)
ALT (U/L)	59.4±70.7 (39.5,5.7-48.6)
AST (U/L)	106.5±98.5 (78.3,15.5-737)
ALB (g/L)	32.6±4.9 (32.4,23.3-49.3)
TBIL (μmol/L)	300.6±178.4 (314,7.8-729)
DBIL (μmol/L)	205.1±124.0 (217.4,3.4-545.2)
BUN (mmol/L)	7.3±5.8 (5.4,1.3-33.7)
CLcr (mL/min)[b]	100.6±45.1 (94.5,17.3-231)
INR	2.38±1.2 (2.1,0.9-5.9)
PT (second)	25.6±9.9 (23.2,11.8-53.9)
PTA (%)	42.9±24.0 (35,13-117)
C_{trough} (mg/L)	3.9±2.5 (3.4,0.06-14.08)
Concomitant medication (PPI)	n (%) of patients
Omeprazole	8 (15.7%)
Esomeprazole	9 (17.6%)
Pantoprazole	6 (11.8%)
Lansoprazole	16 (31.4%)
Genotype distribution frequency	
Ultrarapid metabolizer (UM)	1 (2.0%)
Extensive metabolizer (EM)	24 (47.1%)
Intermediate metabolizer (IM)	21 (41.1%)
Poor metabolizer(PM) Child-Pugh class (A:B:C) MELD score	5 (9.8%) 4:11:36 22.4±10.7(23.8,1-45.5)

PLT count, platelets count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin; DBIL, direct bilirubin; BUN, blood urea nitrogen; CLcr, creatinine clearance rate; INR, international normalized ratio; PT, Prothrombin time; PTA, prothrombin time activity; PPI, proton pump inhibitors;

[a] Results for continuous covariates are presented as mean +-SD [median, range], and results for categorical covariates are presented as frequency (percentage).

[b] According to Cockcroft-Gault formulation.

Table . Population pharmacokinetic parameter estimates from the final model and bootstrap validation

Parameter	Basic model	Basic model	Final model	Final model	Bootstrap	Bootst
	Estimate	**CV%**	**Estimate**	**CV%**	Estimate	**95%CI**
CL (L/h)	1.07	13.0%	0.88	10.5%	0.90	0.74-1.11
V (L)	141.4	8.1%	148.8	7.5%	148.4	129.3-175.5
k_a (h^{-1})	1.1(FIX)	-	1.1(FIX)	-	1.1(FIX)	-
F (%)	86.4	7.5%	88.4	7.5%	89.4	78.1-106.4
PLT on CL	-	-	0.32	21.2%	0.32	0.08-0.52
TBIL on CL	-	-	-0.57	-12.6%	-0.57	-0.72--0.44
WT on V	-	-	1.43	18.0%	1.42	0.86-1.96
ω^2CL	68.3%	25.8%	18.0%	45.3%	18.0%	0.04-0.32
ω^2V	15.3%	22.9%	12.0%	45.6%	12.0%	0.02-0.19
Proportional error	21.8%	10.3%	19.4%	10.0%	19.3%	0.15-0.2

CL, clearance of the central compartment; V, volume of distribution for the central compartment; k_a, first-order absorption rate constant; F, bioavailability; ω^2, variance of inter-individual variability; CV, coefficient of variation, calculated as 100* standard errors/ Parameter Value. CI: confidence interval, 2.5th and 97.5th percentile of the ranked bootstrap parameter estimates.

The final model is: CL(L/h)=0.88×(PLT/65)0.32×(TBIL/314)-0.57xexp(ηCL); V(L)=148.8×(WT/58)1.43×exp(ηV); F(%)=88.4

Table . Probability of C_{trough} attainment after intravenous administration for 30 days in doses of normal liver function patients (Loading dose: 400 mg every 12 hours, maintenance dose: 200 mg every 12 hours)

Loading Doses	Group of TBIL	Probability of C_{trough} attainment	Probability of C_{trough} attainment	Probability of C_{trough} attainment	Probability of C_{trough} attainment	Probability of C_{trough} attainment	Probability of C_{trough} attainment	Probability of C_{trough} attainment
		Intravenous administration	Intravenous administration	Intravenous administration		**Oral administration**	**Oral administration**	**Oral administration**
		<0.5 mg/L	**0.5-5.0 mg/L**	**>5.0 mg/L**		**<0.5 mg/L**	**0.5-5.0 mg/L**	**>5.0 mg/L**
400mg q12h	TBIL-2	0.0%	64.2%	35.8%		0.0%	77.5%	22.5%
	TBIL-3	0.0%	53.2%	46.8%		0.0%	68.1%	31.9%
300mg q12h	TBIL-2	0.0%	91.7%	8.3%		0.0%	96.6%	3.4%
	TBIL-3	0.0%	83.4%	16.6%		0.0%	91.0%	9.0%
200mg q12h	TBIL-2	0.0%	99.8%	0.2%		0.0%	100%	0.0%
	TBIL-3	0.0%	98.8%	1.2%		0.0%	99.7%	0.3%

Table . Probability of C_{trough}attainment after intravenous or oral administration for 30 days according to the recommended dosing regimen (Loading dose: 400 mg every 12 hours, maintenance dose: 100 mg every 12 hours) of voriconazole instructions for mild to moderate patients with liver dysfunction.

Table . Probability of C_{trough} attainment after oral or intravenous administration at different loading doses in TBIL-2 and TBIL-3 patients

Table . Probability of C_{trough} attainment after oral and intravenous administration at different maintenance doses in TBIL-2 and TBIL-3 patients based on a loading dose of 200 mg q12h

Group of TBIL	Dosing inter-vals	Maintenance Doses	Probability of C_{trough} at-tain-ment	Probability of C_{trough} at-tain-ment	Probability of C_{trough} at-tain-ment	Probability of C_{trough} at-tain-ment	Probability of C_{trough} at-tain-ment	Probability of C_{trough} at-tain-ment	Pr of C_t at- tai me
			Intravenous adminis-tration	Intravenous adminis-tration	Intravenous adminis-tration		**Oral adminis-tration**	**Oral adminis-tration**	**Or ad tra**
			<0.5 mg/L	**0.5-5.0 mg/L**	**>5.0 mg/L**		**<0.5 mg/L**	**0.5-5.0 mg/L**	**>5 mg**
TBIL-2	q12h	200mg	0.0%	11.7%	88.3%		0.0%	15.9%	84.
		150mg	0.0%	22.9%	77.1%		0.0%	30.8%	69.
		100mg	0.0%	53.2%	46.8%		0.0%	63.6%	36.
		50mg	0.0%	95.2%	4.8%		0.1%	97.8%	2.1
	qd	200mg	0.0%	59.7%	40.3%		0.0%	69.6%	30.
		150mg	0.0%	80.7%	19.3%		0.0%	87.3%	12.
		100mg	0.2%	95.9%	3.9%		0.3%	97.8%	1.9
		50mg	2.3%	97.6%	0.0%		4.0%	96.0%	0.0
TBIL-3	q12h	200mg	0.0%	6.2%	93.8%		0.0%	7.6%	92.
		150mg	0.0%	9.2%	90.8%		0.0%	11.7%	88.
		100mg	0.0%	17.4%	82.6%		0.0%	24.0%	76.
		50mg	0.0%	65.3%	34.7%		0.0%	76.2%	23.
	qd	200mg	0.0%	20.9%	79.1%		0.0%	27.2%	72.
		150mg	0.0%	37.2%	62.8%		0.0%	47.2%	52.
		100mg	0.0%	70.1%	29.9%		0.0%	80.5%	19.
		50mg	0.0%	98.7%	1.3%		0.1%	99.6%	0.4

Figure legend

Figure 1. Receiver operating characteristic (ROC) curves for predicting adverse events from voriconazole concentrati

Figure 2. Diagnostic goodness-of-fit plots for basic model (A1, A2) and final model (B1, B2). A1 and B1, Observed concentrations versus population-predicted concentrations; A2 and B2, Observed voriconazole plasma concentrations versus individual-predicted concentrations; the lines are the lines of unity y=x.

Figure 3. Diagnostic goodness-of-fit plots for basic model (C1, C2) and final model (D1, D2). C1 and D1, conditional weighted residuals*versus* population-predicted concentrations; C2 and D2, conditional weighted residuals *versus* time.

Figure 4. The median voriconazole C_{trough}versus time profiles for 30 days based on the optimal intravenous (right) or oral (left) dosing regimen. The loading doses of TBIL-1, TBIL-2 and TBIL-3 patients were 400 mg q12h, 200 mg q12h and 200 mg q12h for first day, respectively. The maintenance doses of TBIL-1, TBIL-2 and TBIL-3 patients were 100 mg q12h (squares), 50 mg q12h (filled dots) or 100mg qd (triangles) and 50 mg qd (hollow dots), respectively.