Population Pharmacokinetics and Factors Influencing Trough Concentration of Voriconazole in Children with Hematological Malignancies

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Abstract

Aim: This prospective study aims to investigate the factors influencing voriconazole trough concentration (Cmin), develop a population pharmacokinetics (PPK) model and recommend an appropriate voriconazole dosing regimen for children with hematological malignancies. Methods: Prospectively enrolled a total of 70 children aged <18 years and 149 samples. The factors influencing voriconazole Cmin were analyzed by univariate analysis and multiple linear regression analysis. Nonlinear mixed effects modeling (NONMEM) was applied to establish the PPK model. Dosage simulation based on albumin (ALB) levels and CYP2C19 genotype. Results: Multiple linear regression results demonstrated that route of administration, ALB and concomitant administration with glucocorticoid (GLU) and proton pump inhibitors (PPIs) were significant factors of voriconazole Cmin. A one-compartment model could best describe the pharmacokinetics of voriconazole. The extensive metabolizers (EM), ALB were significant covariates of clearance (CL). The typical value of CL, the volume of distribution (V) and oral bioavailability (F) were 1.52 L/h, 35.7 L and 0.909, respectively. The recommended dosing regimens for EM patients with ALB level of 20.0˜35.0 g/L, 35.1˜45.0 g/L and 45.1˜55.0 g/L were4, 8 and 12 mg/kg intravenously or orally twice daily, respectively, and were 2, 4 and 7 mg/kg by intravenous or oral administration twice daily for non-EM. Conclusion: We found that route of administration, ALB and co-administration of GLU and PPI had quantitative relationships with voriconazole Cmin. The combination of CYP2C19 genotype and ALB levels to determine the initial dosing regimen of voriconazole could provide a reference for individualized treatment in children with hematological malignancies.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

***** Invasive fungal infection dramatically affects the prognosis of patients with hematologic malignancies and is one of the principal causes of death in hematologic malignancies.

***** Voriconazole has a complex pharmacokinetic profile and exhibits different pharmacokinetic characteristics between adults and children.

***** There are still very limited data on the pharmacokinetics and dosing optimization of voriconazole in children with hematological malignancies.

WHAT THIS STUDY ADDS?

***** This study confirmed that ALB, route of administration and concomitant administration with glucocorticoid (GLU) and proton pump inhibitors (PPIs) are significantly associated with voriconazole trough concentration in children with hematological malignancies.

***** The population pharmacokinetics (PPK) analysis demonstrated that the extensive metabolizer, albumin significantly affects voriconazole clearance in children with malignant hematological disease.

***** The dosing regimen based on CYP2C19 genotype and albumin could provide a reference for individualized administration of voriconazole in clinical practice.

ABSTRACT

Aim: This prospective study aims to investigate the factors influencing voriconazole trough concentration (C_{min}), develop a population pharmacokinetics (PPK) model and recommend an appropriate voriconazole dosing regimen for children with hematological malignancies.

Methods: Prospectively enrolled a total of 70 children aged <18 years and 149 samples. The factors influencing voriconazole C_{min} were analyzed by univariate analysis and multiple linear regression analysis. Nonlinear mixed effects modeling (NONMEM) was applied to establish the PPK model. Dosage simulation based on albumin (ALB) levels and CYP2C19 genotype.

Results : Multiple linear regression results demonstrated that route of administration, ALB and concomitant administration with glucocorticoid (GLU) and proton pump inhibitors (PPIs) were significant factors of voriconazole C_{min}. A one-compartment model could best describe the pharmacokinetics of voriconazole. The extensive metabolizers (EM), ALB were significant covariates of clearance (CL). The typical value of CL, the volume of distribution (V) and oral bioavailability (F) were 1.52 L/h, 35.7 L and 0.909, respectively. The recommended dosing regimens for EM patients with ALB level of 20.0˜35.0 g/L, 35.1˜45.0 g/L and 45.1˜55.0 g/L were4, 8 and 12 mg/kg intravenously or orally twice daily, respectively, and were 2, 4 and 7 mg/kg by intravenous or oral administration twice daily for non-EM.

Conclusion : We found that route of administration, ALB and co-administration of GLU and PPI had quantitative relationships with voriconazole C_{min}. The combination of CYP2C19 genotype and ALB levels to determine the initial dosing regimen of voriconazole could provide a reference for individualized treatment in children with hematological malignancies.

1. Introduction

Invasive fungal infection (IFI) is a serious fungal infection caused mainly by Candida and Aspergillus.[1] IFI dramatically affects the prognosis of patients with hematologic malignancies, which is one of the principal causes of death in hematologic malignancies.[2, 3] The Kobayashi et al[4] recorded that the survival rate of pediatric patients with IFI is much lower than that of uninfected patients in hematological malignancies.

Voriconazole is commonly used for the prevention and treatment of IFIs as a triazole antifungal drug with broad-spectrum activity.[5] However, the metabolism of voriconazole in vivo has the characteristics of non-linear pharmacokinetics,[6] and affected by multiple factors such as weight, age, liver function, CYP2C19 genotype and drug interaction, the intra- and interindividual variability in the plasma concentrations is considerable.[7-9] Besides, the poor activity of hepatic drug enzymes in children makes it easier for drugs to accumulate in the body, which leads to more obvious individual differences of plasma concentrations and more complex pharmacokinetics in children.[10] It has been previously demonstrated that there are significant differences in the pharmacokinetic profile of voriconazole between children and adults.[11]Furthermore, pediatric patients with hematological malignancies are vulnerable to myelosuppression and thrombocytopenia during chemotherapy, which will affect the liver metabolism of voriconazole pharmacokinetics.[12] More importantly, the poor metabolizer (PM) of CYP2C19 metabolic in Asians have a higher proportion of distribution compared to other races[13]. These make it impossible for children to be treated according to the recommended regimens for adults or in Europe and the United States.

Population pharmacokinetics (PPK) analysis can assess the basic characteristics of pharmacokinetics and identify the sources of inter- and intra-individual variability[14]. Currently, the published voriconazole PPK models mainly established for adults with invasive fungal infections[15], liver transplantation[16], lung transplantation[17], hematopoietic stem cell transplantation[18] and hematological malignancies[19], while the PPK model of voriconazole in pediatric patients with hematological malignancies has not been reported. Therefore, it is necessary to clarify the pharmacokinetic characteristics of voriconazole in pediatric patients with hematological malignancies and optimize the dosing regimen. This study aims to investigate the factors affecting voriconazole trough concentration (C_{min}), establish a PPK model of voriconazole in children with hematological malignancies and recommend an appropriate voriconazole dosing regimen for children with hematological malignancies.

2 Methods

2.1 Patients and data collection

This single-center prospective study was conducted between June 2019 and September 2020 at the First Affiliated Hospital of Guangxi Medical University, Guangxi, China. We enrolled patients aged <18 years with malignant hematological diseases who received voriconazole intravenously or orally for the prevention or treatment of IFI. The initial dose of voriconazole was administered in accordance with the drug label or the clinician's experience, and adjusted according to the patient's clinical response. The exclusion criteria were: (1) voriconazole failed to reach the steady-state described in the guidelines[20]or was replaced with other antifungal agents during the treatment; (2) undergoing hemodialysis or hemofiltration; (3) allergic to voriconazole.

The following information for patients enrolled are collected: demographics data [gender, age, weight, and body surface area (BSA) etc], laboratory test data [white blood cell count (WBC), neutrophil absolute value (NEU), hemoglobin (HGB), platelet count (PLT), total bilirubin (TBIL), aspartate transaminase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT),Albumin (ALB), alkaline phosphatase (ALP), creatinine (SCR), cystatin C (CYSC), endogenous creatinine clearance (Ccr)] and the concomitant drugs taken during VRC therapy [proton pump inhibitors (PPIs), including omeprazole, esomeprazole, pantoprazole, lansoprazole and rabeprazole, glucocorticoid (GLU), including dexamethasone and prednisone].

2.2 Blood sampling and analytical assays

Blood samples were collected in the morning before dosing when voriconazole reached steady-state. Voriconazole C_{min}were analyzed by enzyme immunoassay technique (EMIT)using Siemens VIVA-E automatic detec-

tor (Siemens healthcare Diagnostic Inc, Newark, USA) with the voriconazole test kit (No.20190401) from Zhuhai Li zhu Reagent Co., Ltd. The kit has a linear range from 0.5˜16 mg/L, possessing good precision (coefficient of variation [?]10%) and accuracy (relative bias within ±15%).

2.3 DNA sequencing and CYP2C19 genetic polymorphism

DNA was extracted with nucleic acid extraction and purification reagent from Baiao Technology Co. Ltd. (Shanghai, China). The CYP2C19 genotyping was performed by DNA Microarray with BR-526-24 -automatic hybridizer from Baiao Technology Co. Ltd. (Shanghai, China). The categories are as follows: (1) Extensive metabolizer (EM) (CYP2C19 *1/*1); (2) Intermediate metabolizer (IM) (CYP2C19 *1 /*2, CYP2C19 *1 /*3); (3) Poor metabolizer (PM) (CYP2C19*2 /*2, CYP2C19 *2 /*3, CYP2C19 *3/* 3)[21].

2.4 Statistical analysis

The determinations of voriconazole C_{min} were analyzed using multiple linear regression. The univariate analysis was used to initially screen variables and P <0.1 as the inclusion criterion. The Pearson or Spearman correlation analysis was used to analyze the correlation between continuous variables and voriconazole C_{min}. Comparison of voriconazole C_{min}among different group were performed by the independent sample t-tests or the Mann- Whitney U-test. The final results with P<0.05 were regarded as statistically significant. All statistical analyses performed using SPSS software (version 20.0, SPSS, Inc. Chicago, IL, USA).

2.5 Population pharmacokinetic analysis

Analysis of PPK were performed by nonlinear mixed-effects modeling software (NONMEM version 7.4.3 ICON Development Solutions, Ellicott City, MD, USA). The first-order conditional estimation with interaction (FOCE-I) option was chosen to evaluate pharmacokinetic parameters and variability. One- and two-compartment structural kinetic models with first-order and Michaelis–Menten elimination were compared during the base model determination step. An exponential model was chosen to describe the inter-individual variability of voriconazole pharmacokinetic parameters. Furthermore, additive, exponential, proportional and combined residual models were used to evaluate the residual variability.

We initially examined the correlation between pharmacokinetic parameters and potential covariates (associated with voriconazole C_{min} in univariate analysis) by visualizing linear plots and box plots. Subsequently, a stepwise forward and backward exclusion approach was used to develop the covariate model. Covariates were considered significant in the case where the following conditions occurred simultaneously: inclusion of covariates resulted in a decrease in the objective function value (OFV) greater than 3.84 ($p< 0.05$) and exclusion of covariates resulted in an increase in OFV greater than 6.64 ($p< 0.01$).

Model evaluation was carried out by Goodness of fit plots (GOFs), visual predictive check (VPC), normalized prediction distribution error (NPDE) and nonparametric bootstrapping analysis (Bootstrap). The GOFs were used to evaluate the adequacy of fitting. The VPC test was performed by 1000 simulations based on the final model to assess the predictive performance of the final model. NPDE could estimate the predictive characteristics of the final model by statistical tests and diagnostic charts. Bootstrap is used to evaluate the robustness and stability of the final model by repeating the original data 1000 times with different random samples.

2.6. Dosing Regimen Simulations

Based on the parameters and covariates obtained from the final model, two CYP2C19 genotype groups: the extensive metabolizers (EM=1) and the non-extensive metabolizers (EM=0) and three ALB groups :20.0 ˜ 35.0 g / L; 35.1 ˜ 45.0 g / L; 45.1 ˜ 55.0 g / L were set respectively (ALB levels in this study ranged from 22.7 to 56.6g/L; median: 34.2 g/L). The dosage regimens of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 mg/kg orally and intravenously every 12 hours were simulated 1000 times for each covariate group (the median and interquartile of body weight collected were used as a fixed value and the dose should not exceed 200 mg/time). The voriconazole C_{min} ranged of 0.5 – 5 mg/L was defined as target range[20]. A higher probability

of target attainment (PTA) regimen with a lower probability of the C_{min}exceeding 5 mg/L was considered to be recommended.

3 Results

3.1 Patients' characteristics

A series of 149 blood concentration samples from 70 patients were enrolled in this study. The median age of the patients was 8.08 years (1.08-17.92). A significant difference was found in voriconazole plasma concentrations, which had a median concentration of 3.37 mg/L (0.03-13.63 mg/L). Patients' characteristics are illustrated in Table1.

3.2 Factors affecting voriconazole trough concentration

As shown in Table 2, the correlation analysis suggested that age, body weight, BSA, HGB, PLT, WBC, TBIL, ALB were associated with voriconazole C_{min} ($P<0.1$). In addition, there is a significant difference of voriconazole C_{min} in the groups of different CYP2C19 genotype, route of administration and concomitant administration with PPIs and GLU ($P<0.1$). The final multiple linear regression results revealed that route of administration, ALB and combined use of GLU and PPIs were the significant factors of voriconazole C_{min}($P<0.05$).

3.3 Population pharmacokinetic analysis

A one-compartment pharmacokinetic model with first-order elimination adequately describes the data. The inter-individual variability and residual variability were all characterized by exponential model.

The analysis of the covariate model confirmed the ALB and EM were the most significant covariates for the clearance (CL) and there were no covariates that had a significant effect on volume of distribution (V). The typical value of CL, V and oral bioavailability (F) of voriconazole obtained in the final model are 1.52 L/h, 35.7 L and 0.909, respectively. The oral absorption rate constant (KA) was fixed to a value of $1.19h^{-1}$.[22, 23] The following formulations are included in the final model: CL (L/h) = $1.52\times1.42^{(EM-1)} \times e^{0.911\times(ALB/34.57)}\times e^{0.254}$; V (L) = 35.7; KA ($h^{-1}$) = 1.19 (fixed); F = 0.909. The PPK parameter estimates of base model and final model are summarized in Table 3.

The GOFs from the final model displayed that the individual-predicted concentration (IPRED) and population-predicted concentration (PRDE) versus detection values (DV) of the final model are close to Y=X (figure 1A and B). Besides, the most conditional weighted residuals (CWRES) are symmetrical distribution on both sides of the line Y=0 and most of points are within ±2(figure 1C and D). The final model's VPC results are presented in Figure 2. Most of the measured values of voriconazole are covered within 90% of the prediction interval (PI), and the predicted value is 5%-95%, demonstrating that the final model possesses good predictive capacity. The results of the final model NPDE statistical tests are as follows: t-test P = 0.77, Fisher test P = 0.343, Shapiro-Wilks test P = 0.117, comprehensive test P = 0.352. The statistical test results combined with the diagnostic chart reveal that the final model exhibited a normal distribution, with excellent stability and predictive performance (Figure 3). In the final model bootstrap verification, 1000 resampled bootstrap data sets were run successfully for 864 times. More importantly, the PPK parameter estimates of the final model showed similar results to the bootstrap results (Table 3), indicating the final model with good robustness and stability.

3.4 Dosage Regimens and PTA Results

The final recommended regimes and its PTA for patients with different CYP2C19 genotypes and ALB levels are shown in Table 4. As the results exhibited, 2, 4 and 7 mg/kg administered intravenously or orally twice daily are recommended for patients (EM=0) with ALB levels of 20.0˜35.0 g/L, 35.1˜ 45.0 g/L and 45.1˜55.0 g/L, with the PTA of 77.72%, 77.07%, 67.22%, 80.09%, 79.77% and 70.86% respectively. For patients (EM=1) with ALB levels of 20.0˜35.0 g/L,35.1˜45.0 g/L and 45.1˜55.0 g/L, the regimens of 4, 8 and 12 mg/kg by intravenous or oral administration twice daily are considered appropriate (the PTA attained 82.67%, 79.42%, 76.80%, 83.40%, 81.12% and 79.54% respectively).

4 Discussion

The factors affecting voriconazole C_{min} and PPK date of voriconazole in pediatric patients with hematologic malignancies are limited. we investigated the factors affecting voriconazole $C_{min}$and successfully developed a PPK model of voriconazole. Most notably, the optimal regimes were recommended based on the final model.

Regarding the influencing factors of voriconazole C_{min}, as reported in adult patients with hematologic malignancies and other pediatric patients[24, 25], voriconazole exhibited a non-linear pharmacokinetic profile. A report of adult inpatients[26] showed no difference in voriconazole concentrations between intravenous and oral administration, which is inconsistent with our results. Karin et al[27] argued that children have a greater metabolic capacity. Another possible explanation is that patients with malignant hematological diseases are prone to nausea and vomiting after chemotherapy. We also found a negative correlation between ALB and voriconazole concentration as reported by previous study[28]. Accordingly, we should be more alert to the effect of ALB levels on voriconazole concentrations, especially in patients with low serum albumin. In terms of concomitant administration, the results of this study showed that combination with PPIs resulted in higher concentrations while Co-administration of GLU resulted in lower concentrations, which is in line with previous studies[29, 30]. Some studies have documented that gender[31], SCR[32], liver function indicators (ALP, AST, ALT, etc.)[28, 33]and CRP levels[34, 35] could affect voriconazole concentrations. However, no significant correlation between these factors and voriconazole concentration were found in this study. The explanation for this may be the difference of race, age and population and further investigation are necessary in the future.

In the part of PPK analysis, the results show that a one-compartment model fits the data best. However, the other studies of children were two-compartment models[36-38], probably due to the fact that pediatric studies are mainly preclinical studies and multicenter large sample studies with a dense sampling strategy, while the sampling strategy of this study was sparse. Fortunately, Farkas et al.[39] compared the accuracy and precision of voriconazole linear, nonlinear, and mixed linear models for prediction. The results suggested that the linear model was slightly more accurate than the other two models, but the differences were minor from a clinical point of view, making all three models suitable for voriconazole.

As summarized in a review of PPK of voriconazole[40], the median of central compartment volume of distribution (V_C) was 1.07 L/kg (0.81-3.26 L/kg), and the interindividual variability of V or V1 and CL was 14.2% (13.6 to 45.4%) and 69.6% (66.5% to 117.4%). These shows that the pharmacokinetic parameters of voriconazole vary significantly among the different pediatric populations, further demonstrating the necessity for individualized dosage in pediatric populations with hematologic malignancies. The population typical values of CL of voriconazole in another pediatric one-compartment model were 2.94 L/h and the apparent volume of distribution was 6.17 L and 7.67 L.[40]However, the typical values of CL and V in this study were only 1.52 L/h and 35.7 L. The possible reasons are as follows: the patients included in this study are patients with hematologic malignancies, who had different degrees of thrombocytopenia and liver dysfunction due to myelosuppression after receiving chemotherapy. However, several studies demonstrated that the reduction of voriconazole elimination is significantly related to liver function[16, 41]. It was also documented in the previous studies that platelet counts were associated with the severity of liver function, where the CL was only 0.88 L/h and 0.58 L/h[12, 42].

The oral bioavailability in this study is 90.9%, higher than 44.6% ~ 73% in other study of children,[22, 23, 43, 44] but lower than 96% and 94.2% in adult.[45, 46] Numerous literatures reported that the oral bioavailability is affected by CYP2C19 genotype, dose, adverse reactions of chemotherapy, such as nausea and vomiting, disease status, gastrointestinal function and diet.[45, 47, 48] A study written by Scholz et al[48] indicated that after intravenous and oral administration of 400 mg voriconazole, the bioavailability of PM was 94.4% (78.8%, 109.9%), while EM was 75.2% (62.9,87.4%). Most notably, the proportion of PM patients in this study is 14.3%, which is much larger than that in Japan and Europe by 2.0% ~ 9.5%.[49, 50] Besides, the bioavailability of 50 mg and 400 mg voriconazole was 39% and 86% respectively from the study by Hohmann et al[6]. These may be the reason why the oral bioavailability of this study is higher than that of other children's studies.

The covariates included in the final model of previous pediatric PPK studies[22, 49, 50] were body weight, CYP2C19 genotypes and ALT. In contrast, the EM and ALB were the significant covariates for the CL of voriconazole, and there were no covariates that had a significant effect on V in the present work. The results of adults with hematological malignancies [19] showed that CYP2C19 genotype significantly affects CL of voriconazole and $AUC_{0\text{-}12h}$ of PM is 2.5 and 1.8 times of EM and IM respectively. In this study, the CL of voriconazole in children with non-EM is reduced by 29.6% compared with EM, which is similar to the 35.5% of another pediatric study.[50] The Wei et al[51] study showed that Low ALB level is significantly correlated with the blood concentration of voriconazole $>$ 5.5 mg/L. Moreover, the study conducted by Dote et al[52] showed that hypoproteinemia (ALB $<$ 30 g/L) is associated with the low CL of voriconazole. Therefore, attention should be paid to monitoring voriconazole blood concentrations in patients with low protein levels and to developing individualized dosing regimens based on ALB levels in conjunction with PPK models to improve treatment efficacy and reduce adverse effects associated with increased blood concentrations.

Currently, there is no recommendation of individualized drug administration for children with hematologic malignancy. In the present study, the dosing was simulated according to CYP2C19 genotype and ALB level. The recommended doses (mg/kg) were4, 8 and 12 mg/kg intravenously o orally twice daily for ALB levels of 20.0˜35.0 g/L, 35.1˜45.0 g/L and 45.1˜55.0 g/L for patients with EM, and were 2, 4 and 7 mg/kg intravenously or orally twice daily for patients with non-EM. The results indicate that higher dose (mg/kg) should be recommended for extensive metabolizer, which is similar to the study of Lin et al[53]. Besides, as described by Prawat et al[54], patents with lower ALB levels were more likely to achieve the target trough concentration. Nevertheless, when the ALB level of EM is 45.1 ˜ 55.0 g/L, the proportion of the concentration $<$ 0.5 mg/L is still high even if the dosage reaches 12 mg/kg in oral or intravenous administration. Hence, whether such patients choose to give high-dose voriconazole or switch to other antifungal drugs in clinical medication remains to be further considered for its efficacy and safety. Overall, the recommended regimen significantly improved the probability of reaching the target trough concentration of 0.5 – 5 mg/L and minimized the probability of the concentration $<$ 0.5 mg/L and $>$ 5 mg/L, which could maximize the efficacy and minimize the adverse reactions of voriconazole in the treatment process.

This study has several limitations: Firstly, due to the limitations of clinical sampling and testing techniques, only a few patients had MIC values, and it was not possible to combine PK/PD parameters AUC0-24h/MIC for dosing regimen development. Secondly, the effects CYP2C9 and CYP3A4 genotype on the pharmacokinetic parameters of voriconazole were not investigated. Finally, this study was a single-center study, whether the findings are applicable to other centers needs to be verified in the future.

5 Conclusion

We confirmed that ALB, route of administration and concomitant administration with GLU and PPIs are significantly associated with voriconazole C_{min}. EM and ALB significantly affect the clearance of voriconazole. The recommend dosing regimens based on CYP2C19 genotype and ALB levels attained 67.22%-83.4% PTA, which could provide a reference for voriconazole individualized treatment in children with hematological malignancies.

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Conflict of interest statement

The authors declared no conflicts of interest concerning the research, authorship, and publication of this article.

Ethical approval

This study was in accordance with the Declaration of Helsinki and national and institutional standards, authorized by the Ethics Committee of The First Affiliated Hospital of Guangxi Medical University (NO.2020-KY-E-018).

Data availability statement

Data for this study are available from the corresponding author under reasonable conditions.

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Table1.Demographic and clinical information

Characteristic	Value [a]
SEX (male/female), n (%)	39/31 (55.7%, 44.3%)
AGE (years)	8.08 (5.10, 15.00)
WT (kg)	24.35 (16.07, 45.50)
Height (cm)	130.00 (103.50, 162.25)
Concentration (mg/L)	3.37 (1.40, 6.02)
BMI (kg/m^2)	16.10 (14.10, 18.08)
BSA (m^2)	0.30 (0.20, 0.56)
HGB (g/L)	79.90 (69.32, 91.25)
PLT (10^9/L)	75.40 (33.90, 189.85)
WBC (10^9/L)	1.57 (0.52, 4.55)
NEU (10^9/L)	0.55 (0.08, 2.78)
TBIL (μmol/L)	8.70 (5.52, 14.00)
GGT (U/L)	45.00 (26.00, 83.25)
ALT (U/L)	19.00 (12.00, 40.50)
AST (U/L)	23.00 (15.00, 35.00)
ALP (U/L)	118.50 (81.75, 160.00)
ALB (g/L)	34.40 (30.42,37.80)

Characteristic	Value [a]
SCR (μmol/L)	25.00(18.50, 37.25)
CYSC (ug/ml)	0.72 (0.60, 0.89)
Ccr (mL/min)	107.97± 28.03
CYP2C19 genotype, n (%)	
EM	32 (45.7%)
IM	28 (40.0%)
PM	10 (14.3%)
Concomitant drugs, n (%)	
PPIs	17 (24.3%)
GLU	20 (28.6%)

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; BMI, body mass index; CYSC, Cystatin C; Ccr, Creatinine Clearance; EM, Extensive metabolizer; GGT, glutamyl transpeptidase; GLU, glucocorticoid; HGB, hemoglobin; IM, Intermediate metabolizer; NEU, Neutrophil; PLT, platelets; PM, Poor metabolizer; PPIs, proton pump inhibitors; SCR, serum creatinine; TBA, total bile acid; TBIL, total bilirubin; WBC, white blood cell count; WT, weight.

[a] Results for continuous covariates are presented as mean ±SD or median (interquartile range), and results for categorical covariates are presented as n (%).

Table2. Results of univariate and multiple regression analysis

variables	Univariate analysis	Univariate analysis	Multiple linear regression	Multiple linear regression
	r	P	β	P
AGE (years)	0.177	0.031*		
WT (kg)	0.183	0.025*		
Dose (mg/kg)	0.112	0.172		
BMI (kg/m2)	0.05	0.548		
BSA (m2)	0.181	0.028*		
HGB (g/L)	-0.29	<0.001*		
PLT (109/L)	-0.283	<0.001*		
WBC (109/L)	-0.184	0.025*		
NEU (109/L)	-0.129	0.117		
TBIL (μmol/L)	0.311	<0.001*		
GGT (U/L)	-0.089	0.281		
ALT (U/L)	0.051	0.54		
AST (U/L)	0.078	0.343		
ALP (U/L)	-0.006	0.939		
ALB(g/L)	-0.418	<0.001*	-0.19	0.000**
SCR (μmol/L)	0.066	0.423		
CYSC (mg/L)	0.005	0.952		
Ccr (mL/min)	-0.02	0.565		
Gender		0.646		
male				
famale				
Route of administration		0.038*		
intravenous			1.801	0.004**
oral				
CYP2C19 genotype		0.038*		
EM				

variables	Univariate analysis	Univariate analysis	Multiple linear regression	Multiple linear regression
IM, PM				
Concomitant drugs				
PPIs		0.004*		
yes			1.985	0.004**
no				
GLU		0.084*		
yes			-1.548	0.004**
no				

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; BMI, body mass index; CYSC, Cystatin C; Ccr, Creatinine Clearance; EM, Extensive metabolizer; GGT, glutamyl transpeptidase; GLU, glucocorticoid; HGB, hemoglobin; IM, Intermediate metabolizer; NEU, Neutrophil; PLT, platelets; PM, Poor metabolizer; PPIs, proton pump inhibitors; r, correlation coefficient; SCR, serum creatinine; TBA, total bile acid; TBil, total bilirubin; WBC, white blood cell count; WT, weight; β,β coefficient.

* P<0.1; ** P<0.05.

Table3.Model parameter estimates and Bootstrap result

Parameters	Base model	Final model	Bootstrap	Bootstrap
	Estimate (RSE)	Estimate (RSE)	Median	2.5%-97.5 %
OFV	388.367	371.647	366.768	287.065-459.722
CL (L/h)	3.23 (12%)	1.52 (37%)	1.59	0.74-3.58
V (L)	39.8 (28%)	35.7 (33%)	35.93	11.91-99.40
KA	1.19	1.19		
F	0.867 (15%)	0.909 (12%)	0.857	0.639-0.990
ϑ_{EM}		1.42 (14%)	1.45	1.10-1.94
ϑ_{ALB}		0.911 (38%)	0.83	0.168-1.527
IIV_{CL} (%)	0.36 (23%)	0.254 (27%)	0.236	0.107-0.424
EPS	0.174 (20%)	0.174 (20%)	0.172	0.108-0.262

ALB, albumin; CL, clearance; EM, Extensive metabolizer; EPS, residual variability; F, bioavailability; OFV, objective function value; RSE, relative prediction error; V, apparent volume of distribution; ϑ, pharmacokinetic parameter; IIV, interindividual variability.

Table4. The PTA of recommended dosing regimens for oral and intravenous administration based on group of ALB and CYP2C19 genotypes

conditions	PTA	PTA	PTA	PTA
	Intravenous administration	Intravenous administration	Intravenous administration	Intraven
	Dose [a]	0.5-5	<0.5	>5
	(mg/kg)	mg/L	mg/L	mg/L
EM=1, ALB=20-35 g/L	4	77.72%	13.04%	9.23%
EM=1, ALB=35-45 g/L	8	77.07%	15.35%	7.58%
EM=1, ALB=45-55 g/L	12	67.22%	29.99%	2.79%
EM=0, ALB=20-35 g/L	2	82.67%	13.17%	4.17%
EM=0, ALB=35-45 g/L	4	79.42%	11.27%	9.32%

conditions	PTA	PTA	PTA	PTA
EM=0, ALB=45-55 g/L	7	76.80%	15.40%	7.80%

ALB, albumin; EM=0, non- Extensive metabolizer; EM=1, Extensive metabolizer; PTA, probability of target attainment.

[a] Dosing every 12 hours

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