Population Pharmacokinetics of Voriconazole and Dose Optimization in Chinese Elderly Patients

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April 26, 2023

Abstract

Objectives: This study aimed to establish a population pharmacokinetic model for elderly individuals receiving intravenous voriconazole, and to assess and optimize the dosing regimens using a simulating approach. Methods: A population pharmacokinetic analysis was conducted using the NONMEN software based on 438 plasma concentrations from 150 elderly patients receiving multiple intravenous doses of voriconazole. The individualized optimal dosage regimen was proposed based on the obtained population pharmacokinetics parameters. The final model was assessed by the goodness of fit plots, non-parametric bootstrap method, and visual predictive check. Monte Carlo simulations were carried out to assess and optimize the dosing regimens with a therapeutic range of 2.0-5.0 mg/L as the target plasma trough concentration (Cmin). Results: A one-compartment model with first-order absorption and elimination fitted well to the concentration-time profile of voriconazole. The typical voriconazole clearance was 3.55 L/h, and the typical volume of distribution was 194 L. Covariate analysis indicated that the CL of voriconazole was substantially influenced by albumin (ALB), gamma glutamyl transpeptidase, and direct bilirubin, while the volume was associated with body weight. Conclusions: The first study on the population pharmacokinetics of voriconazole in Chinese elderly people was performed. Individualized dosing regimens were recommended for different ALB levels based on population PK model prediction. The proposed dosing regimens could provide a rationale for dosage individualization to improve clinical outcomes and minimize drug-related toxicities.
Objectives: The objective of this research was to develop a population-based pharmacokinetic model for the administration of intravenous voriconazole to elderly patients. Additionally, the study sought to evaluate and refine dosing protocols through a simulated approach.

Methods: A study of the population pharmacokinetics of voriconazole was conducted, utilizing NONMEN software and analyzing 438 plasma concentrations taken from 150 elderly patients who received multiple intravenous doses of the medication. The individualized optimal dosage regimen was proposed based on the obtained population pharmacokinetics parameters. The efficacy of the final model was evaluated through a comprehensive analysis that included the examination of goodness of fit plots, non-parametric bootstrap method, and visual predictive check. To further optimize the dosing regimens, Monte Carlo simulations were performed with the goal of achieving a target plasma trough concentration ($C_{\text{min}}$) within the therapeutic range of 2.0-5.0 mg/L.

Results: An accurate fit to the concentration-time profile of voriconazole was achieved by employing a one-compartment model featuring first-order absorption and elimination. The typical clearance rate of voriconazole was found to be 3.55 L/h, with a typical volume of distribution of 194 L. The covariate analysis conducted revealed that albumin (ALB), gamma glutamyl transpeptidase, and direct bilirubin had a significant impact on voriconazole clearance, whereas body weight was associated with the volume.

Conclusions: The first study on the population pharmacokinetics of voriconazole in Chinese elderly people was performed. Individualized dosing regimens were recommended for different ALB levels based on population PK model prediction. The proposed dosing regimens could provide a rationale for dosage individualization to improve clinical outcomes and minimize drug-related toxicities.

Keywords: voriconazole; population pharmacokinetics; dosage optimization; elderly patients

Introduction

The demographic reality of aging is pervasive across the world. According to data published by the National Bureau of Statistics (NBS), 18.7% of China’s population were aged 60 or older by the conclusion of 2021. Extrapolating from this trend, it is projected that approximately 2 billion individuals worldwide will have crossed the age of 60 by 2050. In the course of aging, the physical function and immune system experience noteworthy effects. This results in an increased susceptibility to infectious diseases particularly among older individuals with low immunity, chronic ailments, extended periods of bed rest, prolonged use of strong antibiotics, immunosuppressive agents, and invasive diagnosis and treatment. The administration of broad-spectrum antibiotics and immunosuppression further heightens the vulnerability of elderly patients to fungal infections, which pose life-threatening complications with exceptionally high mortality rates.

Voriconazole (VCZ) is frequently prescribed as a first-line therapy for invasive aspergillosis infections, as per the guideline put forth by the Infectious Diseases Society of America (IDSA), owing to its broad-spectrum triazole antifungal properties. The pharmacokinetics of VCZ are classified as classical and nonlinear, primarily due to the saturation of metabolic clearance and auto-inhibition that varies proportionately with the administered dose. The plasma concentrations of VCZ showed significant individual differences even if administered in the same regimen. According to a multicenter retrospective study carried out by Dolton et al., it was observed that insufficient plasma trough concentrations (<2 mg/L) led to a considerably lower response rate in terms of clinical and radiological parameters. Conversely, supratherapeutic plasma trough concentrations (>5 mg/L) were found to elevate the likelihood of neurotoxicity, visual disturbances, and hepatotoxicity. Enhanced attention to therapeutic drug monitoring (TDM) and personalized medication management is crucial due to the intricate pharmacokinetic characteristics and limited therapeutic range exhibited by voriconazole.

Multiple studies have indicated that age is a significant factor affecting the pharmacokinetics of VCZ. For instance, Niioka et al. discovered that older Japanese patients had higher VCZ trough concentration, and age was also identified as a predictor of VCZ trough levels exceeding 5 mg/L. An analysis of 317 trough concentrations from 166 adult patients revealed that the median trough concentrations of voriconazole in...
elderly patients were significantly higher than those in the adult patients who received VCZ therapy. VCZ undergoes hepatic metabolism mainly via the CYP2C19 isoenzyme, signifying that the pharmacokinetics of this drug are greatly influenced by liver function. Nonetheless, research has shown that advancing age is linked to a slight reduction in alanine aminotransferase (ALT), albumin (ALB), and gamma-glutamyl transpeptidase (GGT) levels, in addition to an increase in bilirubin concentration. These findings suggest that elderly patients may experience a decline in liver function. Moreover, a previously conducted study has indicated that a decline in the liver CYP level could be a contributing factor towards decreases in drug metabolism, which can decrease by as much as 30% once an individual reaches the age of 70. This decrease in liver function significantly reduces the metabolism of VCZ, which leads to excessively high Cmin levels under empirical treatment regimens. Moreover, increased plasma exposure may elevate the risk of adverse reactions related to VCZ. Furthermore, potential hepatotoxicity may further exacerbate liver damage, thus affecting the prognosis of patients. Considering the altered pharmacokinetics typical of the elderly population, VCZ therapy for geriatric patients should be optimized to ensure effective and safe outcomes.

To our knowledge, there is a notable paucity of research pertaining to the pharmacokinetics and dosage optimization of VCZ in the elderly population. The primary objective of this study was to evaluate the VCZ pharmacokinetic properties in geriatric patients via nonlinear mixed effects modeling (NONMEM). The study aimed to ascertain the significant covariates linked to the dynamic changes in VCZ exposure and outline appropriate dose recommendations based on the final model. The intention behind this research is to facilitate the judicious use of VCZ in elderly patients.

Materials and methods

2.1. Study design and ethics

The Nanjing Drum Tower Hospital conducted a retrospective observational study from April 2018 to September 2022. Subjects who met the inclusion criteria were as follows: 1) patients aged 60 years or above, 2) patients who received voriconazole injection (200 mg/bottle, Pfizer Pharmaceutical Co., Ltd) for invasive fungal infections (IFIs), and 3) blood sampling during the steady state for therapeutic drug monitoring (TDM) was available. Subjects were excluded if they met any of the following criteria: 1) patients undergoing continuous renal replacement therapy (CRRT) or extracorporeal membrane oxygenation (ECMO), 2) pregnant women, or 3) other factors deemed unsuitable for this study by the researchers. This study received approval from the Scientific and Research Ethics Committee of the Nanjing Drum Tower Hospital, the affiliated hospital of Nanjing University Medical School, Nanjing, China (No. 2023–075–01), and all procedures were carried out in accordance with ethical standards.

2.2. Data collection and sampling schedule

Demographic data (including sex, age, and body weight) as well as medication information (such as amount, dosing interval, and administration time), co-medication of omeprazole (OME), phenytoin (PTI), pantoprazole (PTO), rabeprazole (RBE), fluconazole (FLU), itraconazole (LTR), rifampicin (RFP), dexamethasone (DXM), prednisolone (PNS) and methylprednisolone (MTL) and laboratory data (white blood cell count (WBC), hemoglobin (HGB), platelet (PLT), globulin (GLO), apolipoprotein A (APOA), apolipoprotein B (APOB), glomerular filtration rate (GFR), ALT, ALB, GGT, aspartate aminotransferase (AST), total protein (TP), alkaline phosphatase (ALP), total bilirubin (TBIL), direct bilirubin (DBIL), creatinine (CR) and creatinine clearance rate (CLCR) were collected via a standardized format utilizing the hospital’s electronic medical record system.

2.3. Quantification of voriconazole concentrations

In this study, the concentrations of voriconazole present in plasma were analyzed using HPLC. Blood samples were collected after administration of at least four doses (on day 3 of treatment) of VCZ to achieve a steady state. A 300 μL sample of plasma was mixed with 600 μL of an acetonitrile solution, which was vortexed for 30 seconds and centrifuged at room temperature for 8 minutes at 15000×g. Following centrifugation, a 200 μL aliquot of the supernatant was injected into the analytical system. A mobile phase
consisting of Acetonitrile: MilliQ water (7.3 v/v) filtered through a 0.45 μm hydrophilic polypropylene filter was used for chromatographic separation on a C18 column (250×4.6 mm, 5μm) at a constant temperature of 40 ºC. The UV detector was set at 262 nm and the overall run time was 8 minutes. The calibration curves demonstrated acceptable linearity over 0.1–30 μg/mL for voriconazole.

2.4. Population pharmacokinetic modeling

2.4.1 Base model

A pharmacokinetic model utilizing nonlinear mixed-effects (base model) software NONMEM 7.3.0 (Globomax, Hanover, MD, USA) was developed. In order to determine optimal structural model selection, one- and two-compartment models with first-order elimination after intravenous administration were evaluated. Exponential error models were implemented to describe symmetrically distributed inter-individual variability (IIV, η) in PK parameters with a mean of zero and a variance of ω². Moreover, to evaluate residual variability (RSV, ε) in VCZ concentrations, additive, proportional, combined (additive plus proportional), and exponential error models were utilized, assuming a symmetrically distributed mean of zero and a variance of σ². Where Cobs is observed value, Cpred is the model-predicted value, and ε, ε’ represents the residual variation.

Additive error model: Cobs = Cpred + ε

Proportional error model: Cobs = Cpred × (1+ε)

Combined error model: Cobs = Cpred × (1+ε) + ε’

Exponential error model: Cobs = Cpred × expε

2.4.2 Covariate screening

Post the establishment of the base model, covariate analysis was performed. Potential covariates and empirical Bayes estimate from the base model were plotted on scatter plots to investigate covariate-parameter relationships. Variables that showed a high correlation coefficient (>|0.5) were not included concurrently in the concluding model to avoid collinearity. The stepwise method was utilized to conduct significant covariate screening. The population median values were used to normalize continuous covariates. In order for a covariate to be deemed significant, the objective function value (OFV, which is defined as -2 times the log-likelihood) had to decrease by at least 3.84 (p<0.05, chi-squared distribution with one degree of freedom) during forward inclusion and increase by at least 10.84 (p<0.001, chi-squared distribution with one degree of freedom) during backward elimination. Additional criteria were used to ensure that the covariates remained intact in the final model, including: 1) minimizing the OFV, 2) improving the goodness-of-fit (GOF), 3) decreasing the differences between individuals as a result of adding covariates, and 4) ensuring the clinical believability of the covariates.

2.4.3 Model evaluation

To evaluate the fitting adequacy of the final model, a Goodness-of-fit (GOF) analysis was conducted utilizing observed concentration (DV) plotted against population-predicted concentration (PRED) and individual-predicted concentration (IPRED), along with conditional weighted residuals (CWRES) plotted against PRED and time. Furthermore, a nonparametric bootstrap analysis was carried out with 1,000 randomly resampled datasets generated from the original data, to assess the stability and reliability of the final model. The resulting average parameter values were compared to the final estimates from the original data set in Table 2. Additionally, a Prediction-corrected visual predictive check (pcVPC) was utilized to graphically evaluate the predictive performance of the final model. This involved simulating concentration profiles 1000 times using the parameter estimates in the final model, and plotting the 5th and 95th percentile concentrations (90% prediction interval) in comparison to the observed concentrations.

An additional 22 patients who satisfied the inclusion criteria were gathered and assessed retrospectively to form an external evaluation group. The precision and accuracy of the model’s prediction were assessed
using various metrics such as relative prediction error (PE), mean prediction error (MPE), mean absolute prediction error (MAPE), and the percentage of |PE|% that lies within 20% (F_{20}) and 30% (F_{30}). The evaluation criteria were MPE [?] ±15%, MAPE [?] 30%, F_{20} > 35% and F_{30} > 50%.

\[
PE (\%) = \frac{C_{\text{pred},i} - C_{\text{obs},i}}{C_{\text{obs},i}}
\]

\[
MPE = \frac{1}{n} \sum_{i=1}^{n} (C_{\text{pred},i} - C_{\text{obs},i})
\]

\[
MAPE = \frac{1}{n} \sum_{i=1}^{n} |C_{\text{pred},i} - C_{\text{obs},i}|
\]

Monte Carlo simulations of dosage regimens

Using Crystal Ball software (Version 11.1.2.4, Oracle Corporation, Redwood Shores, CA, USA), Monte Carlo simulations comprising 10,000 replicates were conducted based on the parameter estimates derived from the final model. The simulations sought to generate plasma concentration-time curves following varied dosing regimens for each subpopulation categorized by ALB levels, with a view to achieving a therapeutic C_{min} range of 2.0-5.0 mg/L. Furthermore, the likelihood of VCZ-related toxicity was evaluated by assessing the probability of the C_{min} exceeding 5 mg/L.

Results

3.1. Patient demographics

In this study, a total of 150 patients, comprising of 438 blood samples, were included and separated into two groups: modeling (consisting of 128 patients and 376 blood samples) and validation (comprising of 22 patients and 62 blood samples). Table 1 displays the demographic and clinical information for the covariates, revealing that the patients had an age range of 60 to 103 years and a weight range of 36.1 to 100 kg. We noted a considerable level of inter-individual variability in C_{min} among the patients, ranging from 0.15 mg/L to 16.8 mg/L. Among the C_{min} values obtained, 42.8% (187/437) of VCZ C_{min} values were maintained within the range of 2.0–5.0 mg/L, whereas 14.4% (63/437) and 42.8% (187/437) of VCZ C_{min} values were below 2.0 mg/L and above 5.0 mg/L, respectively.

3.2. Population pharmacokinetic modeling

The data was well described by a one-compartment model that incorporates first-order absorption and elimination. Notably, the two-compartment model or the non-linear Michaelis-Menten elimination model failed to significantly reduce the OFV or improve the fitting effect relative to the linear one-compartment model. The exponential error model was found to be the optimal method for fitting individual variability in PK parameters, while a residual variability additive model proved effective in describing residual variability.

The methodology employed in the stepwise covariate modeling procedure yielded a finalized model that consists of significant covariates for CL/F, namely ALB ([?OFV= -14.495], GGT ([?OFV= -9.965], and DBIL ([?OFV= -7.091]. It was observed that V was significantly influenced by body weight (WT, [?OFV= -12.614), as demonstrated by the stepwise covariate modeling procedure. The population parameters estimated for the final model are presented in Table 2 and the equations of the final model are as follows:

\[
CL (L/h) = 3.22 \times \exp((ALB-33.55) \times 0.0422) \times (GGT/71.65)^{0.294} \times \exp((DBIL-4.6) \times (-0.0136)) \times \exp(\eta_{CL})
\]

\[
V = 194 \times \exp((WT-63) \times 0.0337) \times \exp(\eta_{V})
\]

3.3. Model evaluation

Figure 1 displays the customary GOF diagnostic plots, demonstrating satisfactory correlation between the IPRED and PRED with the observed value. The CWRES versus time and PRED scatter appears to be in
good shape, with the majority of points located within the range of ±2 (Figure 1). The bootstrap outcomes indicate a strong reliability of the final model, with 959 out of 1,000 bootstrap trials being successful. Furthermore, it should be noted that all parameter estimates aligned with the standard values of the definitive model, while the 95% confidence interval fully coincided with the final model’s parameters (as detailed in Table 2), which serves as a compelling indication of the robustness of the final model. Figure 2 illustrates the VPC results, where the observed median (solid line) and observed 5th and 95th percentiles (dashed lines) were situated reasonably within the simulation-based prediction intervals (shaded areas). This indicates that the final model shows acceptable predictive performance. The external validation yielded MPE and MAPE values of 12.3% and 38.4%, respectively. The data further reveals that F20 represents 32.8% of the total, while F30 accounts for 50.8%, indicating superior performance. Overall, the final model demonstrated good precision and accuracy, in line with the aforementioned evaluation criteria.

3.4. Monte Carlo simulations of dosage regimens

A Monte Carlo simulation that incorporated inter-individual variability (IIV) and residual variability (RSV) was employed to identify the most appropriate VCZ dosage regimens. The final model parameters were used to conduct simulations of VCZ trough concentrations at steady-state conditions. Each dosage regimen underwent a total of 10000 Cmin replicates. The recommended target trough concentration range of 2.0–5.0 mg/L, as suggested by Hamada et al. was adopted. According to the final model, it was determined that ALB served as a significant covariate contributing to VCZ CL. The ALB levels were stratified based on a cutoff resembling the median observed level of 33.55 g/L (range 3.4–56.75), and CL values were analyzed accordingly. As shown in Figure 3, patients with ALB levels ≤35 g/L exhibited a significantly lower VCZ CL (mean: 2.78 L/h) compared to those with ALB levels >35 g/L (mean: 4.02 L/h) (P < 0.001). In the ≤35 g/L group, nearly all patients achieved the target trough concentration range of 2.0-5.0 mg/L with a 100 mg intravenous maintenance dose twice a day. Conversely, patients in the >35 g/L group required higher doses to attain comparable target concentrations as the ≤35 g/L group. 150 or 200 mg twice daily may be a more suitable option for patients in this group, as shown in Figure 4.

4. Discussion

The pharmacokinetic model is an effective tool for clinical therapy and is becoming more crucial for optimizing customized dosage regimens. The limited therapeutic index and rather large systemic inter-individual variability of VCZ make its clinical use more challenging. Prior research has shown that target therapeutic exposures to VCZ were not adequately achieved in a variety of clinical scenarios using typical VCZ dosage regimens. 43.3% of the patients receiving intravenous medication had concentrations that were outside the acceptable therapeutic range, according to a population pharmacokinetic analysis by Hope et al. Population pharmacokinetic strategies for VCZ dosage may improve therapeutic decision-making more individualized, which is vital in vulnerable patients.

The aim of this investigation was to examine the population pharmacokinetic features of VCZ among older Chinese patients, analyze the impact of demographic, biological, and medication variables on voriconazole pharmacokinetics, and establish ALB, GGT, and DBIL as significant covariates for the clearance of voriconazole, with weight affecting the volume of distribution. The finalized model delineated typical population values of pharmacokinetic parameters as follows: TVCL = 3.55 L/h, TVV = 194 L. TVCL in this study was lower than in previous models which were constructed based on adults, at the same time, the TVV was higher than them, which may be ascribed to the physiological and pathological changes in elderly patients. The resulting model’s stability and predictability were shown to be rather excellent by GOF charts, bootstrap calculations, and pcVPC findings. External validation results revealed that the MPE and MAPE of the elderly patients were 12.1% and 37.8%. As far as current information can provide, our study represents the initial external and methodical assessment of the VCZ pharmacokinetic model’s predictive efficacy in the elderly demographic.

Although the voriconazole displayed a non-linear pharmacokinetics characteristic, which was related to the saturable clearance mechanisms, the pharmacokinetics of voriconazole in the population were primarily...
characterized using linear models consisting of either one or two compartments. Taking into consideration that non-linear VCZ elimination tends to occur mostly at extremely high dosages exceeding 10 mg/kg/d, it can be inferred that its influence on the predictive accuracy in our population would not be significant.\textsuperscript{30} The results were reinforced by Farkas et al.'s comparative investigation that evaluated the precision and exactitude of three distinct structural models (linear, nonlinear, or mixed linear and nonlinear) for VCZ. By examining 519 samples from 67 patients, their outcomes demonstrated that the linear model performed slightly superior to the other models in terms of accuracy. One-compartment models rather than two-compartment models were ultimately selected as the basic structural model in this investigation due to the modest difference in the OFV.

There exists significant evidence indicating that the decreased elimination of VCZ is linked to compromised liver function, as evidenced by fluctuating levels of various biochemical markers including ALT, AST, GGT, AKP, ALB, TBIL, and DBIL. Moreover, it has been reported that a reduction in liver CYP level may lead to a decline in drug metabolism by nearly 30\% after the age of 70.\textsuperscript{20} Based on this, we have postulated that elderly patients may exhibit higher than usual levels of voriconazole trough concentration due to their compromised liver function. The impact of these trough concentrations on hepatotoxicity has been thoroughly studied, and it has been revealed that the incidence of hepatotoxicity rises from 4.2\% for lower serum concentrations to 12.4\% for supratherapeutic concentrations.\textsuperscript{31} It is noteworthy that high VCZ trough concentrations can be detrimental to liver health and may result in metabolic disorders and higher VCZ exposure. This feedback mechanism might worsen the prognosis of patients. Hence, clinicians must accord priority to patients with liver dysfunction during their routine practice.

According to this investigation, there was a significant correlation between the clearance rate of VCZ and the levels of ALB, GGT, and DBIL. These findings are consistent with those presented by Chantharit et al.\textsuperscript{32} Due to the moderate binding between voriconazole and ALB (42–58\%), voriconazole pharmacokinetics may be significantly correlated with ALB because of its impact on voriconazole distribution. On the other hand, low amounts of albumin as a drug carrier limit the drug's metabolism in the liver and lower its clearance rate. In comparison research by Cheng et al. in 2020, the albumin concentration was significantly lower in the elderly cohort than those in the adult cohort. Therefore, the CL of voriconazole in elderly patients is lower than in adults, which leads to a higher plasma concentration. The correlation between the GGT concentration and VCZ CL has been partially established, as evidenced by the backward deletion step revealing a significant increase of -2LL value (26.22). However, it is noteworthy that the impact of this correlation is relatively low and is overshadowed by the effects of ALB. The concentration of plasma TBIL had a significant impact on the protein-protein binding of VCZ, as evidenced by Vanstraelen et al.\textsuperscript{33} Previous studies have indicated that TBIL levels were associated with the clearance of VCZ in patients with liver dysfunction,\textsuperscript{21} and were considered to be an independent factor affecting VCZ concentration\textsuperscript{34,35}. However, our own findings reveal that levels of DBIL, rather than TBIL, had an effect on VCZ pharmacokinetics. The liver contains a smooth endoplasmic reticulum (ER) replete with enzymes that metabolize various drugs, including VCZ. DBIL undergoes bioconversion to indirect bilirubin (IBIL) within the ER, and DBIL levels may reflect the status of the ER, thereby showing a correlation to VCZ metabolism.

The capacity of tissue protein binding is a significant factor influencing the volume of drugs in the body. Our study confirms that the volume of voriconazole increases with WT, which is consistent with the findings of Lin et al\textsuperscript{36}. VCZ has high lipophilicity and low water solubility, with its absorption being affected by the digestion of fats and the formation of lipid micelles due to its lipid-water partition coefficient (log P) of 2.1.\textsuperscript{37} However, clinical practice does not support body weight-adjusted dosing in adults, as the variability of VCZ pharmacokinetic profiles was not improved with a body weight-adjusted dose compared to a fixed dose. This finding is supported by several studies on obese patients,\textsuperscript{38} which reported that obese patients exhibit elevated concentrations of serum, comparable to those of normal subjects, when administered a fixed dose of medication regardless of difference in body weight.\textsuperscript{39} Hence, dosing based solely on actual body weight may not be feasible, especially for obese patients.

According to the Monte Carlo simulation, patients with serum albumin levels of 35 g/L or lower have
a higher likelihood of achieving the desired trough concentration compared to those with ALB levels above 35 g/L. These findings align with the observed decrease in clearance (CL) capacity in patients with hypoalbuminemia. The findings indicate that decreased ALB levels may heighten VCZ exposure, and patients experiencing hypoproteinemia may necessitate elevated dosage levels beyond standard clinical treatment. Furthermore, the percentage of VCZ $C_{\text{min}}$ > 5.0 mg/L considerably rose with escalating doses. To conclude, the proposed medication regimen can enhance the efficiency and safety of VCZ therapy and perform as a reference aid for clinical applications.

The current study has several limitations that should be noted. First, this study was retrospective with a relatively small sample size, and possible bias may exist in the recording time of administration and blood collection. Second, the majority of samples collected were trough concentrations, which may not fully reflect the absorption and distribution characteristics of VCZ, and made it difficult to estimate the pharmacokinetics of VCZ. Third, information on the genetic information such as CYP3A4 and CYP2C19 polymorphism which have been demonstrated to be significant factors impacting the pharmacokinetics of VCZ were not collected since testing is not routinely performed.

5. Conclusion

According to our knowledge, this study is the first VCZ population PK investigation carried out in Chinese elderly patients. The clearance of voriconazole was shown to be highly influenced by ALB, GGT, and DBIL, whereas the volume was associated with WT. Monte Carlo simulation was performed based on different ALB levels, and the suggested regimens may offer a theoretical framework for tailoring doses to improve clinical outcomes while minimizing drug-induced adverse effects. Therefore, simultaneous monitoring of serial ALB and VCZ levels may be a significant and practical approach to setting a rational dosage regimen for elderly patients.

Acknowledgments

This work was supported by National Natural Science Foundation of China (Grant No.82104316), Nanjing Medical Center for Clinical Pharmacy, Jiangsu Research Hospital Association for Precision Medication (Grant No. JY202231) and Nanjing Pharmaceutical Association – Changzhou Siyao Hospital Pharmaceutical Research Fund project (Grant No. 2022YX006).

CRediT authorship contribution statement


Conflict of Interest Disclosure

The authors declare that they have no known competing financial interests.

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