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Article

Whole-body physiology-based pharmacokinetics of caspofungin for general patients, intensive care unit patients and hepatic insufficiency patients

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Abstract

Caspofungin is an echinocandin antifungal agent licensed as a first-line therapy for invasive candidiasis in patients with moderate to severe illness or recent exposure to azoles. In this study we developed a whole-body physiology-based pharmacokinetics (WB-PBPK) model to predict the pharmacokinetics (PK) of caspofungin, and combined with Monte Carlo simulation (MCS) to optimize clinical dosage regimens of caspofungin in different kinds of patients. A WB-PBPK model of caspofungin was built and validated with raw data from 4 previous trials of general patients, intensive care unit (ICU) patients with Child-Pugh B, ICU patients on continuous renal replacement therapy, mild and moderate hepatic insuffciency (HI) patients. MCS was used to optimize clinical dosage regimens of caspofungin in these patients. A cumulative fraction of response (CFR) value of ≥90% was considered to be the minimum for achieving optimal empirical therapy. The simulated results of the WB-PBPK model were in good agreement with observed values of all trials. For general and ICU patients with caspofungin 70/50 mg, AUC and Cmax were decreased with the increase of body weight (BW) and showed great variation. MCS showed all general patients achieved CFR≥90% regardless of BW. But not all ICU patients with higher BW (≥70 kg) could achieve CFR≥90%. Compared with standard dosage regimens in general patients, caspofungin 70/35 mg in ICU patients with Child-Pugh B achieved significantly decreased AUC and C_{max}, but obtained similar AUC and C_{max} in moderate HI patients with Child-Pugh B. The WB-PBPK model of caspofungin is able to predict PK of all populations correctly. The combined WB-PBPK model with MCS can successfully optimize clinical dosage regimens of caspofungin in all patient populations.

Keywords: caspofungin; antifungal agent; whole-body physiology-based pharmacokinetics model; intensive care unit; hepatic insuffciency; cumulative fraction of response

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Introduction

Caspofungin is an echinocandin antifungal agent licensed as a first-line therapy for invasive candidiasis in patients with moderate to severe illness or recent exposure to azoles[1]. The recommended dosage regimen of caspofungin is a loading dose of 70 mg followed by 50 mg daily (70/50 mg), administered intravenously over 1 h. Caspofungin is highly protein bound (96%) and metabolizes slowly in the liver[2-4]. Its liver uptake is a biphasic process and its binding to the surface of hepatocytes is fast and reversible. Studies demonstrated that the uptake of caspofungin by liver is related to the active organic anion transporting polypeptide 1B1 (OATP1B1)[5]. The plasma clearance (CL) of caspofungin is 10 to 12 mL/min[2]. It is eliminated mainly by hepatic, for only one to two percent of the antifungal agent is through renal clearance[6]. The elimination of caspofungin from plasma is slow and the half-life of caspofungin is 9–11 h[2].

Clinically, pharmacokinetics (PK) parameters in intensive care unit (ICU) patients are often different from those in healthy subjects[7]. Factors associated with alterations in PK include changes in organ function, use of extracorporeal clearance techniques and drug interactions[8, 9]. It was also reported that caspofungin plasma concentrations were influenced by hypoalbuminaemia and hepatic impairment (HI)[7]. One study demonstrated that caspofungin trough plasma concentrations

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(C_{min}) ranges were relatively wide in surgical ICU patients and influenced by protein binding[7]. Another study showed that caspofungin area under the curve (AUC) was increased by 55% and 76% in patients with mild and moderate HI, respectively[4, 10]. But at present, data are very limited and absent on these special patients, an increase in knowledge on these patients should be considered. Clinically, patients weighing >80 kg are advised to receive a dosage regimen of 70/70 mg[11]. But studies of general ICU population and hematopoietic stem cell transplantation patients found that body weight (BW) (range 50–99 kg) had no effect on caspofungin PK[9, 12]. Whether age and race could influence the PK of caspofungin is not clear. On the other hand, one study demonstrated that the vast majority of fungal infections are caused by *Candida* spp[9]. In the critically ill, the infections of invasive *Candida* spp. are associated with high crude and attributable mortalities as high as 60% and 40%, respectively[13]. One multicentre observational study in Spain had carried out that mortality was associated with age, *Candida* spp., different from *C. parapsilosis* and inadequate treatment[14]. All of these ask for a model which could predict the PK of caspofungin in different populations (general patients, ICU patients and HI patients) with different physical conditions, BW, age, race, *Candida* spp. And based on the PK parameters, a Monte Carlo simulation (MCS) could be used to optimize the clinical dosage regimens of caspofungin in different patient populations.

Whole-body physiology-based PK (WB-PBPK) modellings consider the physical and chemical characteristics of a drug and it also give thorough consideration of physiological processes of drug absorption, distribution, metabolism and elimination accurately[15]. Based on a series of parameters, such as physiological and physicochemical properties, CL, distribution into tissues and metabolism or active transport, WB-PBPK could predicts PK of a drug[15]. Then based on a series of equations, we can develop a WB-PBPK model which could be applied to forecast disease dependencies[7, 9], BW, age, and race can also be used to investigate the variability expected in different patient populations[6, 12].

The aim of the present study was to build and verify a WB-PBPK model which could predict the PK of caspofungin in general patients, ICU patients with Child-Pugh B, ICU patients on continuous renal replacement therapy (CRRT) and HI patients, then to evaluate the impact on the PK of caspofungin between different individuals through stochastic simulations of different body weight, age and race using the validated WB-PBPK model. Finally, combined with MCS technique to help in the selection of a safe and effective administration scheme after simulation of the potential exposure and disposition in different patient populations.

Materials and methods

PK data

Clinical PK data for intravenous administration of caspofungin in healthy adults and all patients were obtained from the literature[4, 9, 10, 16, 17]. Raw data of 20 healthy subjects, receiving single intravenous doses of 20 mg, 40 mg, 70 mg, 100 mg, respectively, were used for model development. The mean age was 29 years (range, 21–39 years) and the mean weight was 75 kg (range, 60–88 kg). The observed mean concentrations of caspofungin over time were from the literature[4]. Mean concentrations of caspofungin over time from a double-blind, placebo-controlled, serial-panel study of 24 healthy male subjects to investigate the pharmacokinetics of caspofungin following daily doses of 15, 35, or 70 mg were used to validate the model[4]. Another trial of caspofungin in healthy subjects studied the standard dosage regimen of 70/50 mg[10]. Plasma drug profiles defined by concentrations at 0 h (predose) and at 0.5, 0.75, 1, 1.25, 1.5, 2, 4, 8, 12, and 24 h postdose were obtained on days 1 and 14. Intervening trough (24-h postdose) concentrations (C_{min}) were obtained prior to dosing on d 3, 4, 7, and 10[4]. The relevant data are shown in Table 1.

To develop and qualify the WB-PBPK model in general patients[16], ICU patients with Child-Pugh B[9] and ICU patients on CRRT[17], HI patients[10], raw data from 4 clinical trials were used. The study description, population included, treatment schedule, doses and sampling scheme are shown in Table 1. The study of general patients was a formal phase II dose escalation trial in patients with invasive aspergillosis. Caspofungin was administered once daily as an iv infusion over 120 min at 70 mg (9 patients), 100 mg (8 patients), 150 mg (9 patients) and 200 mg (20 patients). Pharmacokinetic sampling was performed serially on d 1 (2, 3, 5–7 and 24 h after the infusion started) and peak (at the end of infusion) and trough levels (immediately before the next infusion started) were collected on d 4, 7, 14 and 28. All observed data from pharmacokinetic sampling were pooled as mean±standard deviation[16]. Depending on the WB-PBPK model, we studied the recommended dosage regimens (70/50 mg in ICU patients, mild HI; 70/35 mg in moderate HI patients) of caspofungin[9,10,17]. To evaluate the model, we collected 508 trough concentrations from 161 patients (39 ICU patients with Child-Pugh B, 16 ICU patients on CRRT, 47 moderate HI patients and 68 mild HI patients) of the First Affiliated Hospital of Xi'an Jiaotong University. The pharmacokinetic sampling were pooled as mean± standard deviation in ICU patients and HI patients. The study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University. All subjects signed the informed consent before any screening item being performed.

Model development

The WB-PBPK model of caspofungin, which was built by GastroPlus version 9.0 (Simulations Plus, USA), was used for all of the simulations in healthy subjects. The WB-PBPK (disposition) model was composed of a number of tissue compartments which were linked together by venous and arterial blood circulation. These compartments include the heart, lung, brain, adipose, muscle, skin, liver, kidney, and so on. The drug distribution into different compartments was driven by perfusion-limited kinetics for all of the tissues were considered to be well-stirred compartments. Each compartment was defined by an associated tissue blood flow rate, volume and a tissue to-plasma partition coefficient. We used the built-in

Table 1. Overview of the clinical studies used for model development and for comparison with model predictions.

Study No	Study description	Population	Treatment schedule	Dose	Sampling scheme	Ref
1	Double-blind, randomized, placebo-controlled, rising-single-dose, three-period study	Healthy subjects	Initial single-dose study	20 mg (*n*=6), 40 mg (*n*=6), 70 mg (*n*=6), 100 mg (*n*=5)	Plasma was collected at 0 h (predose); at 30, 45, 60, 75, and 90 min; and at 2, 3, 4, 6, 9, 12, 24, 48, 72, 96, 144, and 216 h following the start of drug infusion	[4]
2	Double-blind, placebo-controlled, serial-panel, rising-multiple-dose study	Healthy subjects	Initial multiple-dose study	15/15 mg (*n*=5), 35/35 mg (*n*=5), 70/70 mg (*n*=6)	Plasma drug profiles defined by concentrations at 0 h (predose) and at 0.5, 0.75, 1, 1.25,1.5, 2, 4, 8, 12, and 24 h postdose were obtained on days 1 and 14. Intervening trough (24-h postdose) concentrations (C_{24h}) were obtained prior to dosing on days 3, 4, 7, and 10	[4]
3	Multiple-dose study	Healthy subjects	Multiple-dose study	70/50 mg (*n*=8)	Blood samples were obtained at 0, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 9, 12, and 24 h postdose from the start of caspofungin infusion on days 1, 7, and 14	[10]
4	A formal phase II dose escalation study	General patients	Multiple-dose study	70/70 mg (*n*=9), 100/100 mg (*n*=8), 150/150 mg (*n*=9), 200/200 mg (*n*=20)	Caspofungin PK sampling was performed on day 1 (immediately prior to dosing and 2 h [peak level], 3 h, 5 to 7 h, and 24 h [trough level] after the start of infusion) and at peak and trough time points on days 4, 7, 14	[16]
5	Open-label, Phase IV, multiple-dose, multicentre observational trial	ICU patients with Child Pugh B	Multiple-dose study	70/50 mg (*n*=21)	A PK curve was drawn on day 3 (+1) of treatment at t=0 (pre-dose) and 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h post-infusion. For quantification of intraindividual variation a second PK curve was drawn on day 7 (+1) at t=0 (pre-dose) and 1, 4, 8, 12 and 24 h post-infusion	[9]
6	Multiple-dose study	ICU patients on CRRT	Multiple-dose study	70/50 mg (*n*=15)	Blood samples of 2 ml were drawn from an arterial line at 1, 2, 4, 8, 12, and 24 h after the start of caspofungin infusion	[17]
7	Multiple-dose study	Patients with hepatic insufficiency	Multiple-dose study	Mild HI patients (*n*=8, 70/50 mg) Moderate HI patients (*n*=8, 70/35 mg)	Blood samples were obtained at 0, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 9, 12, and 24 h postdose from the start of caspofungin infusion on days 1, 7, and 14	[10]

mass balance differential equations to develop the model[18].

Vital physicochemical parameters and the key vitro data for caspofungin are depicted in Table 2. The pK_a, Rbp, solubility-pH, effective permeability and particle size were obtained using the ADMET Predictor™ module of GastroPlus. Human log*P*, fup (plasma unbound drug) was obtained from the related literature[19, 20]. The tissue-to-plasma partition coefficients of caspofungin were calculated using established tissue-composition based models. Total plasma CL of caspofungin was calculated by the PKplus model of the GastroPlus version 9.0 (Table 3). The results of non-compartment model will be used to develop the WB-PBPK model. The main elimination route of caspofungin is hepatic (98%) and only two percent of caspofungin is through renal clearance. So the CL data of liver and renal used in the model will based on this. The simulation time was 144 h and the volume of dosage administration was 250 mL.

PK simulations

Based on the raw data from 4 clinical trials, we developed and qualified the WB-PBPK model in general patients, ICU patients with Child-Pugh B and ICU patients on CRRT and HI patients. The study description, population included, treatment schedule, doses and sampling scheme were recorded and used in the development and verification of the WB-PBPK models. Total plasma CL from different populations were calculated by the PKplus model of the GastroPlus version 9.0 (Table 3). The results of non-compartment model were used to develop the WB-PBPK model. The simulation time were 14 d and the volume of dosage administration were 250 mL.

Model evaluation

To evaluate the WB-PBPK models, a visual comparison between the predicted data of GastroPlus version 9.0 and the observed data (literature resources and our research data) of the different trials from different populations was carried out. Goodness of fit (GOF) plots were performed to analyze the accuracy between simulated and observed data. The prediction error (PE) was estimated according to Eq. 1[19].

$$PE=(simulated-observed)/observed\times100 \quad (Eq.1)$$

The fold-error, which represents the difference between observed and predicted *in vivo* values, was used to assess the accuracy of the predicted PK parameters, and if the fold-error was less than two, the prediction was considered successful[21, 22].

$$Fold\text{-}error=observed/predicted \text{ (observed value > predicted value)} \quad (Eq.2)$$

$$Fold\text{-}error=predicted/observed \text{ (observed value < predicted value)} \quad (Eq.3)$$

Model application

Virtual trial simulations

For general and ICU patients, we simulated the recommended dosage regimens (70/50 mg) of caspofungin. On the other hand, other two multiple dosage regimens (70/35 mg, 70/70 mg, 100/100 mg) of caspofungin were simulated to investigate the effects of different dosage regimens of caspofungin in these patients.

For HI patients, except the recommended dosage regimens (70/35 mg for moderate HI patients, 70/50 mg for mild HI patients), dose reduction of 50/25 mg and dose escalating of 70/70 mg, 100/100 mg were simulated using the WB-PBPK model.

PK variability of varying body size of the recommended dosage regimens of caspofungin in general patients, ICU and HI patients were assessed by creating virtual populations weighing 40–100 kg. Virtual ages of 18–95 years were simulated in these patients, too. What's more, different race groups, representatives of Asian and Westerner were simulated. Based on the WB-PBPK model, we could obtain the PK parameters including peak plasma concentrations (C_{max}), C_{min}, AUC and CL of these patients under different weight conditions.

Dosage optimization

To describe caspofungin pharmacokinetic/pharmacodynamics (PK/PD) adequacy for the treatment of invasive *Candida* spp. and determine whether the different dosage regimens

Table 2. Physicochemical and *in vitro* data for caspofungin used in the simulations.

Parameter	Value	Source
Molecular weight	1093.3	Estimated by ADMET Predictor™
log*P*	0	[25]
PK_a	10.74 (acid), 9.73 (base)	Estimated by ADMET Predictor™
Solubility (mg/mL)	18.58	Estimated by ADMET Predictor™
pH for solubility	10.25	Estimated by ADMET Predictor™
Effective permeability (P_{eff}, cm/s)	171	Estimated by ADMET Predictor™
Mean precipitation time (s)	900	Estimated by ADMET Predictor™
Diff. Coeff (cm^2/s)	3.4×10^4	Estimated by ADMET Predictor™
Drug particle density (g/mL)	1.2	Estimated by ADMET Predictor™
Fup (Plasma unbound drug, %)	3	[26]
Rbp (Blood/Plasma concentration ratio)	0.55	Estimated by ADMET Predictor™

Table 3. Observed and simulated pharmacokinetic parameters of caspofungin after intravenous administration of different dosing regimens in healthy adults, general patients, ICU patients with Child Pugh B, ICU patients on CVVH and CVVHD and hepatic insufficiency patients.

Patients	Dose	CL_{total} (L/h)			*V*(L)			$t_{1/2}$ (h)			$AUC_{0\text{-}24\ h}$ (mg·h/L)			C_{max}		
		Observed	Predicted	Fold-error	Observed	Predicted	Fold-error	Observed	Predicted	Fold-error	Observed	Predicted	Fold-error	Observed	Predicted	Fold-error
Healthy volunteers	20 mg[a]	0.65	0.55	1.18	—	7.14	—	10.72	7.61	1.41	30.97	30.76	1.01	3.06	2.79	1.10
	40 mg[a]	0.72	0.57	1.26	—	7.14	—	9.64	7.61	1.27	55.6	61.52	1.11	6.17	5.58	1.11
	70 mg[a]	0.59	0.56	1.05	—	7.14	—	9.29	8.39	1.11	118.45	118.61	1.00	12.04	10.27	1.17
	100 mg[a]	0.74	0.70	1.06	—	7.14	—	8.61	6.64	1.30	134.11	134.20	1.00	14.03	13.85	1.01
	15/15 mg[b]	0.55	0.58	1.05	—	7.33	—	8.60	9.23	1.07	24.37	22.57	1.08	2.79	2.45	1.14
	35/35 mg[b]	0.66	0.62	1.06	—	7.33	—	9.51	7.69	1.24	54.9	53.01	1.04	5.97	5.36	1.11
	70/50 mg[b]	0.55	0.52	1.06	—	6.47	—	10.58	7.44	1.42	100.47	96.15	1.05	9.94	9.97	1.00
	70/70 mg[b]	0.55	0.56	1.02	—	6.53	—	10.70	8.22	1.30	144.27	133.83	1.08	15.42	12.19	1.26
	100/100 mg[c]	—	0.53	—	—	6.52	—	—	8.23	—	—	188.68	—	—	17.41	—
General patients	70/70 mg[b]	0.40	0.43	1.07	—	6.46	—	—	11.17	—	170	162.79	1.04	13.8	14.05	1.02
	100/100 mg[b]	0.40	0.38	1.05	—	7.46	—	—	12.90	—	243	263.16	1.08	19.7	18.68	1.05
	150/150 mg[b]	0.40	0.41	1.03	—	6.62	—	—	11.96	—	365	375	1.03	29.6	29.02	1.02
	200/200 mg[b]	0.40	0.39	1.02	—	6.71	—	—	11.59	—	487	489.8	1.01	39.4	39.32	1.00
ICU patients with Child Pugh B	70/35 mg[c]	—	0.47	—	—	7.05	—	—	11.42	—	—	74.46	—	—	6.50	—
	70/50 mg[b]	0.54	0.45	1.2	7.72	7.12	1.08	18.49	11.54	1.60	107.2	111.11	1.04	8.65	8.43	1.03
	70/70 mg[c]	—	0.45	—	—	7.34	—	—	11.25	—	—	155.55	—	—	11.47	—
	100/100 mg[c]	—	0.46	—	—	7.26	—	—	11.30	—	—	218.39	—	—	16.95	—
ICU (CVVH patients)	70/50 mg[b]	0.46	0.45	1.02	8.34			12.4	12.35	1.01	107	111.11	1.04	11.0	8.66	1.27
ICU (CVVHD patients)	70/50 mg[b]	0.36	0.38	1.06	8.84			15.2	14.98	1.01	141	131.57	1.07	10.8	9.71	1.11
Mild HI patients	70/35 mg[c]	—	0.43	—	—		—	—	12.08	—	—	81.39	—	—	6.53	—
	70/50 mg[b]	0.47	0.41	1.15	—		—	11.71	12.03	1.03	107.59	121.95	1.13	9.15	8.89	
	100/100 mg[c]	—	0.46	—	—		—	—	11.96	—	—	217.39	—	—	16.98	—
Moderate HI patients	50/25 mg[c]	—	0.27	—	—		—	—	15.36	—	—	92.59	—	—	5.76	—
	70/35 mg[b]	0.30	0.28	1.07	—		—	15.07	16.34	1.08	116.22	125	1.08	8.82	8.17	1.08
	70/50 mg[c]	—	0.28	—	—		—	—	16.32	—	—	178.57	—	—	10.98	—
	70/70 mg[c]	—	0.29	—	—		—	—	16.65	—	—	280	—	—	15.28	—

[a] Single doses study.
[b] Multiple doses study.
[c] Virtual doses study.

of caspofungin could achieve PK/PD targets in the general patient populations, ICU and HI patients. A MCS method was performed using the simulated data of WB-PBPK model. Through virtual simulation of Gastroplus, we obtained the AUC of different dosage regimens of these special patients. The MCS methods, the pharmacodynamic targets for *Candida* species ($fAUC_{0\text{-}24}$/MIC ratio for *C. albicans*, *C. glabrata* and *C. parapsilosis*) and the minimum inhibitory concentration distributions for *Candida* species have been described previously[23]. The optimal dosage regimens were evaluated to compare the simulated probability of target attainment (PTA) and cumulative fraction of response (CFR) in these subjects. A CFR value of ≥ 90% was considered to be an appropriate empirical dosage regimen.

Results

Caspofungin PK

The WB-PBPK model for caspofungin was established according to the scheme of relevant tissue compartments of the disposition model. Simulations were conducted based on the physicochemical and *in vitro* data of caspofungin (Table 2). Hepatic and renal caspofungin CL (Table 3) were calculated by the PKplus model, as described in the method section.

The observed (literate resources data) and mean simulated plasma concentration-time profiles of caspofungin in healthy subjects are vividly presented in Figure 1. The accuracy of the predictions are summarized in Table 3. The predicted PK parameters were nearly consistent (<2-fold error) with the observed values (literate resources data). Accurately, using the *in silico* data, *in vitro* data, WB-PBPK model could simulate the plasma concentration-time profile following intravenous administration and predicted CL as inputs to the model, as shown in Figure 1 and Table 3.

Data verification

The established WB-PBPK model of caspofungin could predict the observed concentration-time profile (literate resources data) for all dose groups of different populations accurately (Figures 1–3, Supplementary Figure 1). For all doses levels, the simulated peak concentrations seem to be underrated by 20% but they were within the error range. As shown in Supplementary Figure 1, the predicted concentration-time-curve was in accordance with the observed mean values (literate resources data) of healthy subjects with the multiple doses administration of 15/15 mg, 35/35 mg, 70/50 mg and 70/70 mg, which is the same to general patients with the dosage regimens of 70/70 mg, 100/100 mg, 150/150 mg and 200/200 mg (Figure 2). According to the GOF plot, we could see a good accuracy between predicted and observed data (literate resources data, Supplementary Figure 2A–B). Only the simulated peak concentrations were undervalued in Gastroplus. For ICU patients with Child-Pugh B, ICU patients on CRRT and HI patients, when using the WB-PBPK distribution model to simulate plasma concentrations, a reasonable match to the measured concentration range was observed (Figure 3). The GOF plot showed a good accuracy between predicted

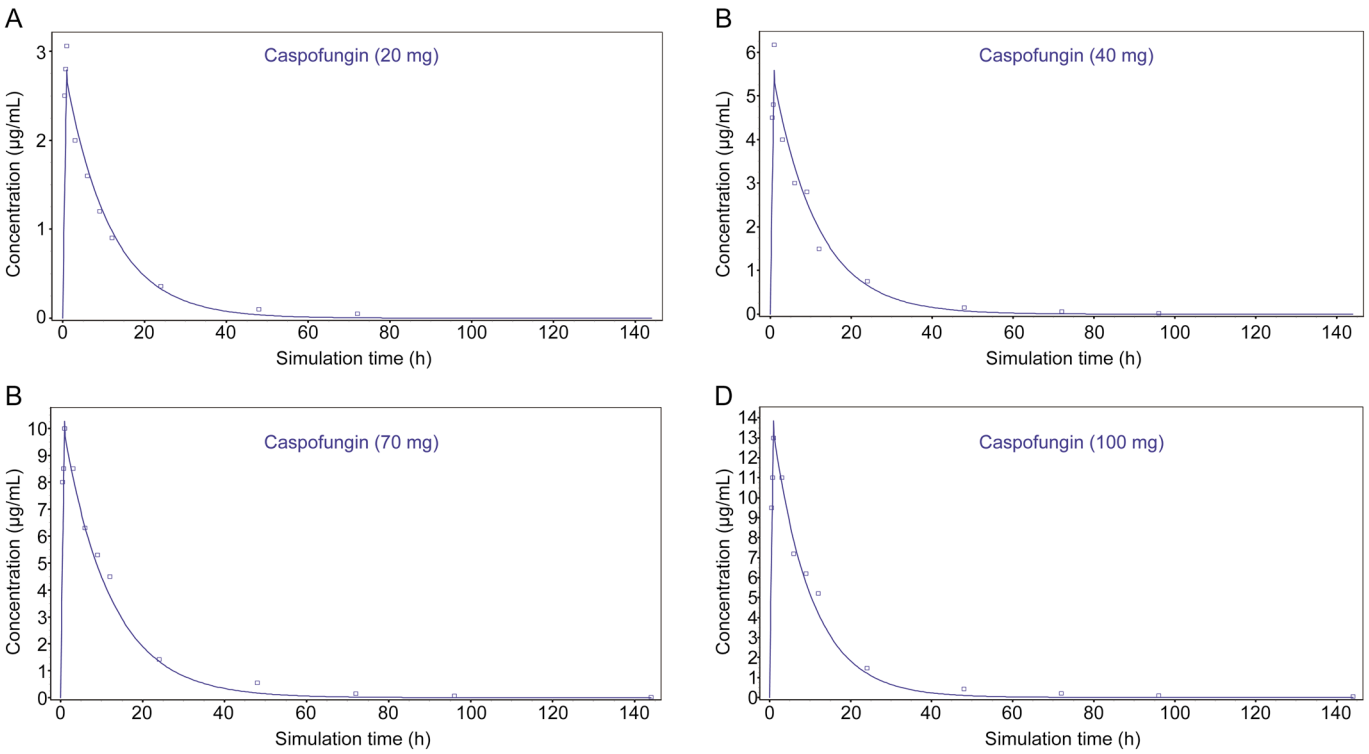

Figure 1. Simulated (line) and observed[4] (square) plasma concentration-time profiles of caspofungin after 20 mg (A), 40 mg (B), 70 mg (C) and 100 mg (D) single dose intravenous administration in healthy subjects.

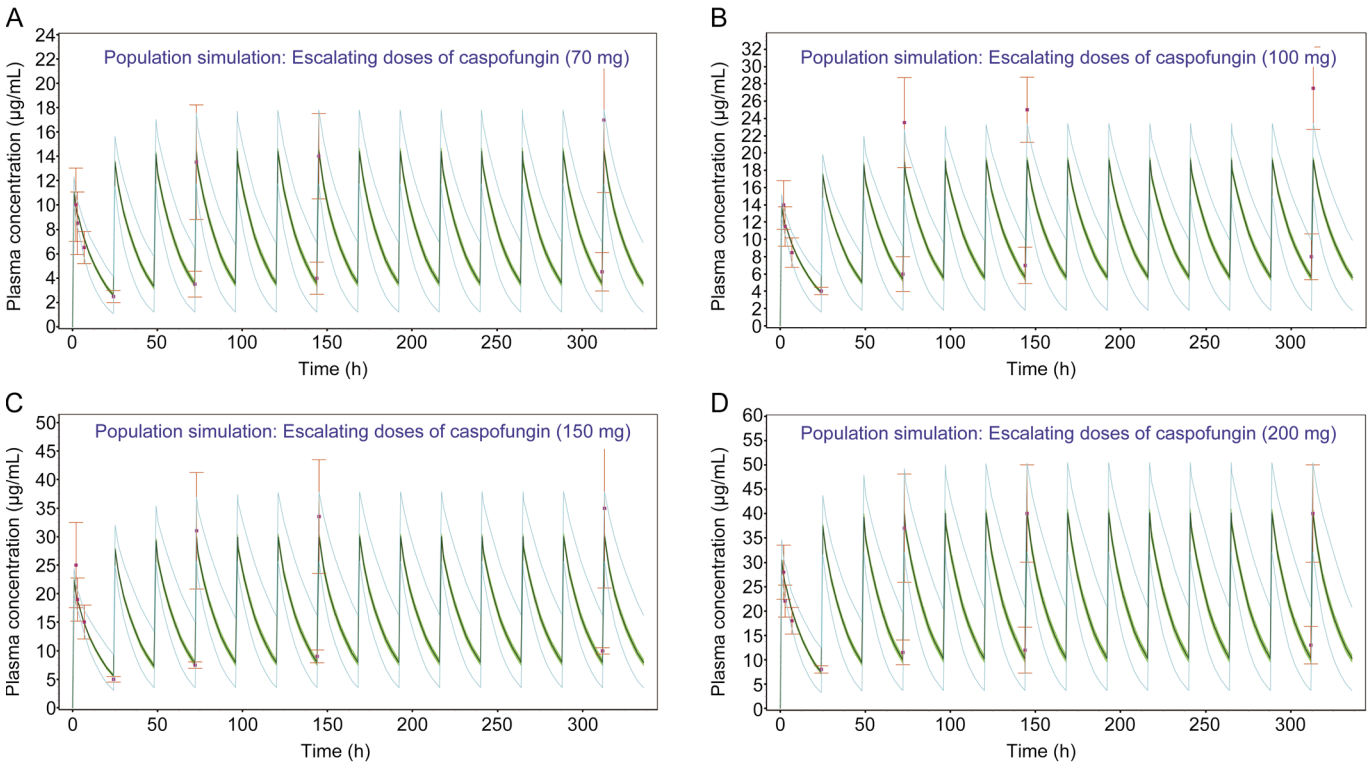

Figure 2. Simulated and mean observed (symbol±SD)[16] plasma concentration-time profiles of caspofungin after 70/70 mg (A), 100/100 mg (B), 150/150 mg (C) and 200/200 mg (D)[16] intravenous multiple doses in general patients. A solid thick line adjacent to the middle of the concentration-time profile represents the mean of the predictive values. Solid squares represent the observed clinical concentration-time data[16]. The shaded area represents the 90% confidence interval for the simulated data, and the thin lines on either hand represent individual simulated results of the 100% range of simulated individual data.

and observed data (literate resources data, Supplementary Figure 2C–D). The simulated peak levels seemed to be underestimated by 10%, which were within the error range. The simulated trough levels seemed to be underestimated by 10% in ICU patients with Child Pugh B and 5% in ICU patients on CRRT and mild HI patients compared with the observed data (literate resources and our research data), for moderate HI patients, it showed a sufficient accuracy between predicted and observed data. The CL, V_{ss}, $t_{1/2}$, AUC, C_{max} of different patients with different dosage regimens are shown in Table 3. The fold-error of all dosage regimens were less than 2.

Virtual trial simulations

PK parameters of general patients and ICU patients are shown in Table 3. Particularly, the PK parameters of ICU patients were recorded. At steady state, the AUC of 70/35 mg, 70/70 mg, 100/100 mg of caspofungin in ICU patients were 74.5 mg·h/L, 155.5 mg·h/L, 218.4 mg·h/L, respectively. The AUC of moderate HI patients were 92.6 mg·h/L, 178.6 mg·h/L, 280 mg·h/L after simulation of the reduction dose of 50/25 mg and dose escalating of 70/70 mg, 100/100 mg.

Supplementary Figure 3A, 3B and 3C showed the relationship between C_{max}, C_{min}, AUC, CL and BW with caspofungin 70/50 mg in general patients and ICU patients and 70/35 mg in moderate HI patients, respectively. We find that C_{min} were constant in all investigated virtual patients and did not correlate to BW or other covariates. This was also valid for the CL. But C_{max} and AUC began a slow decline with the increase of body weight. The variation tendency was not obvious in HI patients.

As shown in Supplementary Figure 3D, patients with different ages showed no statistical difference in PK parameters. Compared with Westerner, C_{max} in Asian showed a slight increase and C_{min} showed a slight decrease in all of these general patients, ICU patients and HI patients (Supplementary Figure 4).

Optimization of the clinical dosage regimens

The WB-PBPK model coupled with a MCS showed the currently recommended dosage regimens of caspofungin in all patients achieved CFR ≥ 90% for *C. albicans* and *C. glabrata,* but achieved CFR ≤ 65% for *C. parapsilosis*, a maintenance dose of 100/100 mg in ICU and mild HI patients and 70/70 mg in moderate HI patients achieved CFR ≥ 90% for *C. parapsilosis* (Figure 4 and Table 4).

Disscussion

Drug research based on the mathematical models becomes extremely important for the optimization of clinical dosage regimens in special populations, mostly by providing rea-

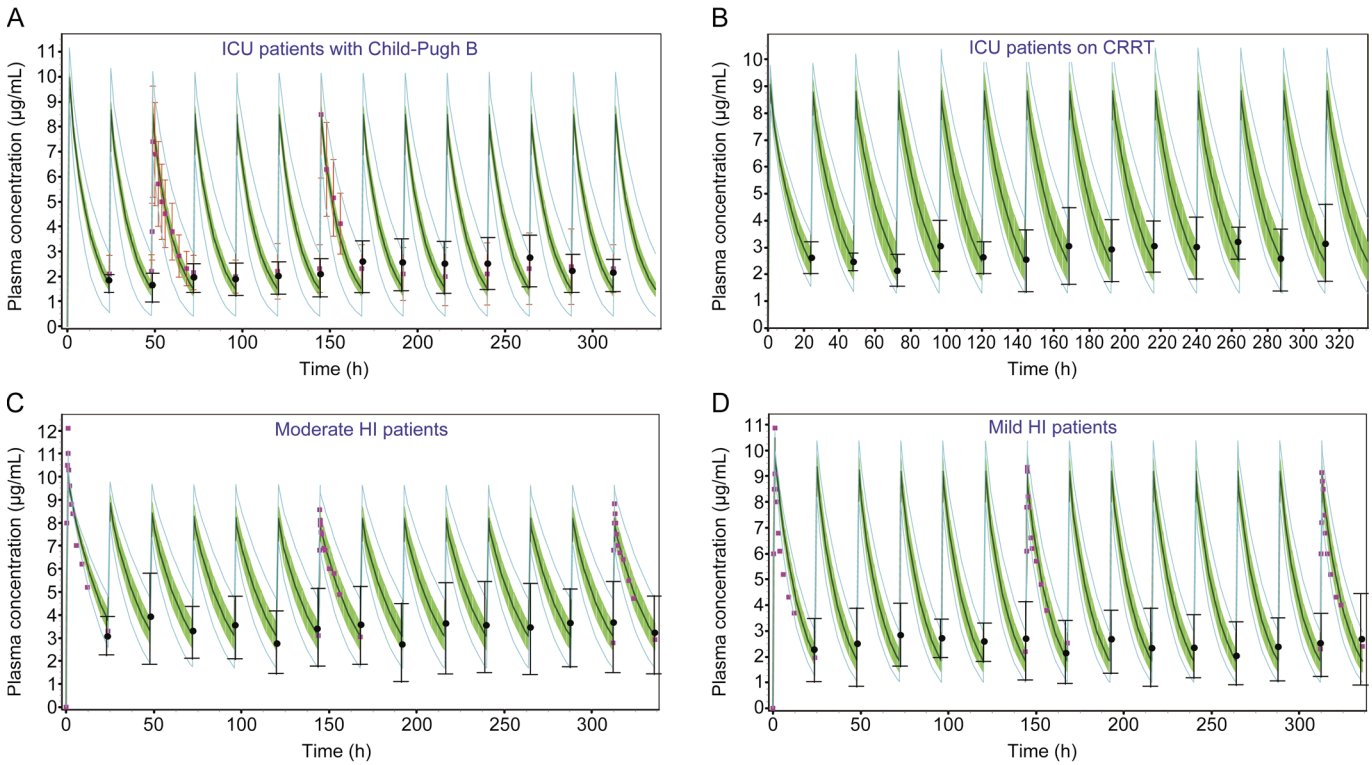

Figure 3. Simulated and mean observed (symbol ± SD) plasma concentration-time profiles of caspofungin after the recommended intravenous multiple doses in ICU patients with Child-Pugh B(A)[9], ICU patients on continuous renal replacement therapy (CRRT) (B)[17], moderate (C) and mild HI patients (D)[10]. A solid thick line adjacent to the middle of the concentration-time profile represents the mean of the predictive values. Solid squares represent the observed clinical concentration-time data[9, 17, 10], and solid circles represent our data of trough concentrations (mean±SD). The shaded area represents the 90% confidence interval for the simulated data, and the thin lines on either hand represent individual simulated results of the 100% range of simulated individual data.

sonable dose selection method and thereby offer a reliable way to evaluate the risks and benefits. At present, WB-PBPK models have been used for prediction of the pharmacokinetics in special populations for their strength in data integration and delivery of mechanistic insights and superior predictive power[24]. These models could explain phenomenons from the perspective of mathematical model principles and can be applied to forecast disease dependencies and can also be used to investigate the variability expected in different patient populations[24]. Based on the WB-PBPK models, this investigation focus on the influence of disease state on the PK of caspofungin. But most importantly, the study makes innovation in combining WB-PBPK model with MCS to optimize the clinical dosage regimens in special patients.

This article first describes the use of WB-PBPK modelling to assist research and clinical study of PK of caspofungin in ICU patients and HI patients. The approach which integrated drug-specific parameters such as log$P$, pK_a, solubility and permeability and *in vitro* data such as plasma protein binding and blood-to-plasma concentration ratio was able to simulate the pharmacokinetics of caspofungin across multiple dose levels in different human populations with suitable accuracy. The methodology also provided a reliable way to understand the mechanisms underlying the pharmacokinetic processes of caspofungin considering the influence of weight, age and race. Based on the changes of caspofungin pharmacokinetic parameters and combined with MCS, an optimization of dosage regimens was developed in these special patients.

After WB-PBPK simulation, we find that for ICU patients on CRRT, the PK parameters from the WB-PBPK simulation were in good agreement with those of the observed (our research data). When combined with MCS method, the recommended dosage regimen (70/50 mg) is appropriate in these patients. But caspofungin maintenance dose should not be reduced to 35 mg in ICU patients with Child-Pugh B which based on the Child-Pugh score if this classification is driven by hypoalbuminemia as it results in significantly lower exposure. A dosage reduction to 35 mg daily following the 70 mg loading dose is reasonable for moderate HI patients with Child-Pugh score B. If the maintenance dose was reduced to 25 mg/d, C_{max} will decrease (Mean: 5.5 mg/L, data were from the model simulation), which would affect the therapeutic effect of caspofungin. On the other hand, a maintenance dose increased to 50 mg/d will lead to a higher C_{min} of 4.2 mg/L (data were from the model simulation), which would induce adverse reactions during the period of treatment.

With the increase of BW, PK of echinocandins might be altered due to changes in volume of distribution and/or CL.

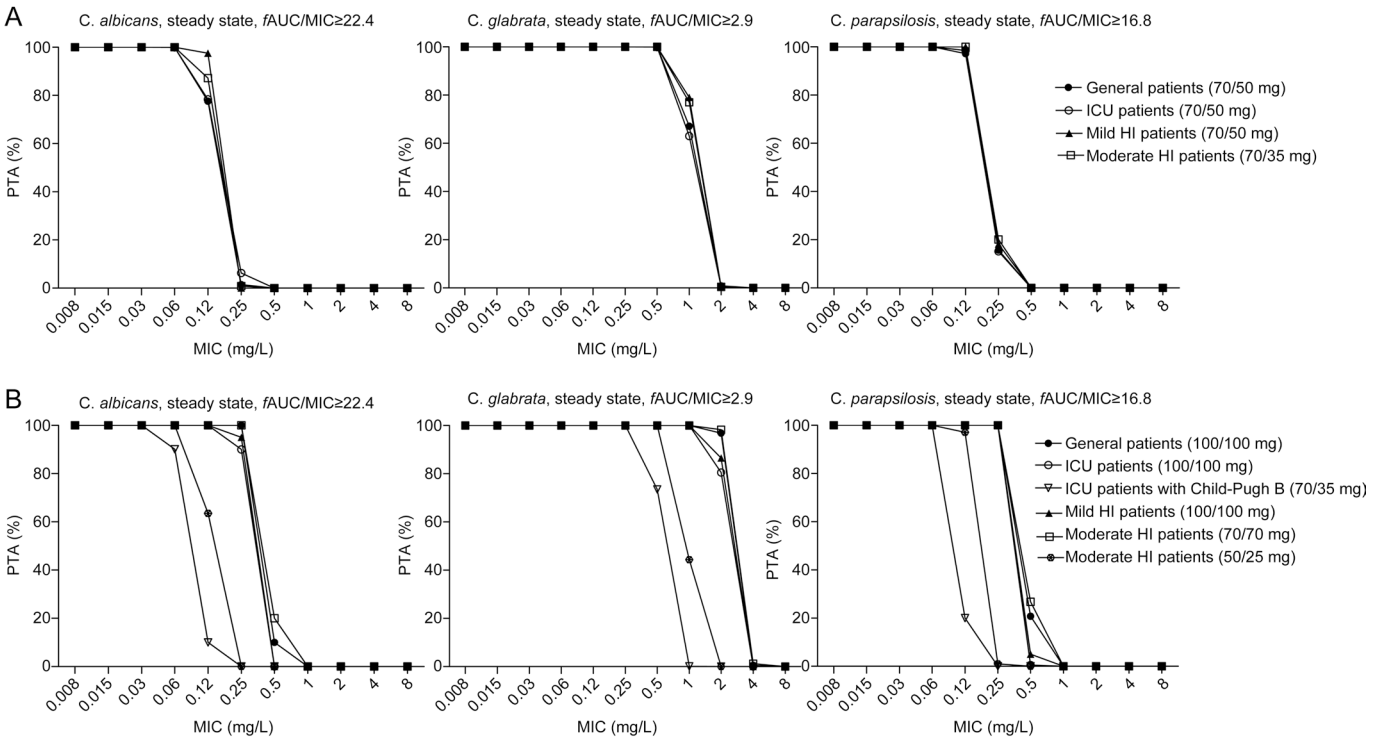

Figure 4. Figure 4A were PTA for *C.albicans*, *C.glabrata*, *C.parapsilosis* of the recommended dosage regimens of caspofungin in general patients, intensive care unit (ICU) patients (including ICU patients on CRRT and ICU patients with Child-Pugh B), mild hepatic insufficiency (HI) and moderate HI patients. The recommended dosage regimens of caspofungin for general patients (solid circles), ICU patients (hollow circles) and mild HI patients (solid triangles) were 70/50 mg, and for moderate HI patients (hollow squares), the recommended dosage regimen was 70/50 mg. Figure 4B were PTA for *C. albicans*, *C. glabrata*, *C. parapsilosis* of the adjustive dosage regimens of caspofungin in general patients (100/100 mg, solid circles), ICU patients (100/100 mg, hollow circles), ICU patients with Child-Pugh B (70/35 mg, downward hollow triangles), mild HI (100/100 mg, upward solid triangles) and moderate HI (70/70 mg, hollow squares; 50/25 mg, a circle with a fork in it) patients. The pharmacodynamic index was *f*AUC/MIC.

Studies have shown that PK in obese patients might be altered due to a change of more fat tissue in relation to BW, change in liver metabolism and an increase in CL, and change in plasma protein constituents should also be considered[25-27]. Clinically, PK data of echinocandins in obese patients are scarce. One study demonstrated that patients weighing >80 kg are advised to receive caspofungin 70/70 mg[28]. In surgical ICU patients, weighing >75 kg were advised to receive a dosage regimen of 70/70 mg for lower C_{min} (decreased by 28%) were predicted in these patients[7]. But in general ICU populations and hematopoietic stem cell transplantation patients (BW: range 50–99 kg) were discovered have no effect on caspofungin PK[9, 12]. With the WB-PBPK simulation, our study demonstrated that general and ICU patients weighing >70 kg are advised to receive 70/70 mg. But no dose adjustment is needed for mild and moderate HI patients weighing >70 kg for the recommended dosage regimens (70/50 mg for mild HI patients and 70/35 mg for moderate HI patients) could achieve CFR ≥ 90% for most *Candida* spp., such as *C. albicans* and *C. glabrata*. For adult patients, age has no effect on the PK of all these patients, there

Table 4. Cumulative fraction of response % (CFR %) of caspofungin against *Candida spp*. in three different kinds of people.

Dosing regimens (mg/d)[a]	*C. albicans*				*C. glabrata*				*C. parapsilosis*			
	General patients	ICU patients	Mild HI	Moderate HI	General patients	ICU patients	Mild HI	Moderate HI	General patients	ICU patients	Mild HI	Moderate HI
70/50 mg	96.3	96.8	97.9	—	99.5	99.4	99.5	—	67.3	66.5	68.9	—
70/35 mg	—	86.9	—	98.2	—	98.8	—	99.5	—	20.9	—	69.3
50/25 mg	—	—	—	93.3	—	—	—	98.4	—	—	—	63.9
70/70 mg	—	—	—	99.8	—	—	—	99.8	—	—	—	93.5
100/100 mg	99.6	99.4	99.3	—	99.7	99.8	99.7	—	92.9	91.2	90.9	—

[a] All dose regimens are virtual dosage regimens.

is also no need for dose adjustment in old patients. Compared with Westerners, C_{max} in Japanese showed a slight increase and C_{min} showed a slight decrease in all of these general patients, ICU patients and HI patients (Supplementary Figure 4). But no dose adjustment is needed.

WB-PBPK model coupled with MCS showed that the current recommended dosage regimens of caspofungin in all patients achieved CFR ≥ 90% for *C. albicans* and *C. glabrata*, but achieved CFR ≤ 65% for *C. parapsilosis*. The dosage regimens of 100/100 mg in ICU and mild HI patients and 70/70 mg in moderate HI patients achieved CFR ≥ 90% (Figure 4). So for *C. albicans* and *C. glabrata* in all patients, the recommended dosage regimens are reasonable. For *C. parapsilosis*, dosage regimens of 100/100 mg in ICU and mild HI patients and 70/70 mg in moderate HI patients are needed.

Assignment of metabolism to transporters in the model is not considered in this paper but would be necessary for more detailed conclusions about the sources of variability in caspofungin PK. This would also require careful consideration of the demographics of the studied population and of other sources of variability. One study demonstrated that the intake approach of caspofungin into the liver is a biphasic process with a fast, reversible binding to the surface of hepatocytes and a slow transport through the active OATP1B1[5]. Clinically, effective and reliable data on transporters and enzymes from *in vitro* experiments are needed in WB-PBPK models[29], but we did not obtain utilizable K_M and V_{max} values of OATP1B1 for the transport of caspofungin in the literature. So data of V_{max} and K_M *in vitro* is urgently needed to refine the WB-PBPK model of caspofungin. Another limitation of this study is that the data for the model verification were almost from the literate resources and we acquired them from the manuscripts, but not given by the original authors. In order to make up for the defects, we collected 508 trough concentrations from 161 patients (39 ICU patients with Child-Pugh B, 16 ICU patients on CRRT, 47 moderate HI patients and 68 mild HI patients) to evaluate the model and found that they all showed sufficient accuracy between predicted and observed data.

Conclusion

In conclusion, a WB-PBPK model for caspofungin was developed and qualified in diverse adult population groups. The model successfully predicted the intravenous and PK of caspofungin across multiple dose levels in normal human populations and special patients. This represents a case study that highlights the prospective applications of the WB-PBPK model combined with the MCS to provide clinical PK predictions and optimize the clinical dosage regimens. PK of caspofungin can be obtained before proceeding with clinical studies. Clinically, when BW is higher than 70 kg in ICU patients, an increasing maintenance dose of 70 mg every day should be considered in humans at lower exposures. Dose reduction of caspofungin in ICU Patients with Child Pugh B will result in suboptimal exposure. In the future, combined with other methods, the model could be used as a basis for further clinical investigations to enable a priori adjustment of drug dosing for maximal efficacy and minimal toxicity.

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Author contribution

Ya-lin DONG designed the study and edited the manuscript; Qian-ting YANG contributed to the analysis, interpretation, manuscript writing, and final approval of the manuscript; Ya-jing ZHAI contributed to the conception and design, analysis, interpretation, manuscript writing, and final approval of the manuscript; Lu CHEN contributed to the data collection, analysis, interpretation, manuscript writing, and final approval of the manuscript; Tao ZHANG, Yan YAN, Ti MENG, Lei-chao LIU, Li-mei CHEN, Xue WANG contributed to the conception and design, data collection, interpretation, manuscript writing, and final approval of the manuscript; All authors read and approved the final manuscript.

Supplementary information

Supplementary information is available at the website of Acta Pharmacologica Sinica.

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