Body Surface Area-Based Dosing Regimen of Caspofungin in Children: a Population Pharmacokinetics Confirmatory Study

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ABSTRACT We evaluated the population pharmacokinetics of caspofungin in children (2 to 12 years of age). The real-world data from 48 children were best fit by a two-compartment model with first-order elimination. Subsequent covariate analysis demonstrated that body surface area had a significant correlation with caspofungin pharmacokinetics, compared to body weight. The population pharmacokinetics of caspofungin confirmed that adjustment of caspofungin dosage based on body surface area is most appropriate for pediatric use.

KEYWORDS caspofungin, children, developmental pharmacokinetics, dose

Caspofungin has been approved by the U.S. Food and Drug Administration and the European Medicines Agency as therapy for invasive candidiasis and aspergillosis in pediatric patients (1–4). Pharmacokinetic and safety studies of caspofungin have been performed in infants, toddlers, and children (5–8) and support a body surface area (BSA)-based dosing regimen in labeling. However, there are limited clinical trial or real-world studies on caspofungin population pharmacokinetics and dosing adaptations in pediatric populations. To date, only one population pharmacokinetic study has analyzed a set of covariates; it found that body weight and disease state were significant covariates affecting caspofungin pharmacokinetics (8). BSA and body weight were not independently incorporated into the model, however, and it is impossible to judge their impact. These limited data and controversial results highlight the need for population pharmacokinetic studies of echinocandins in children and precise quantification of body weight and BSA effects on pharmacokinetics. Thus, the purpose of our study was to define the population pharmacokinetics of caspofungin in children 2 to 12 years of age and then to confirm the caspofungin dosing regimen for use in such patients.

A prospective, open-label, pharmacokinetic trial was performed at Robert Debré Hospital (Paris, France). The study protocol, including sampling, was approved by the institutional review board of Robert Debré Hospital, and written informed consent was obtained from the parents or guardian of each patient. All patients received 70 mg/m² (loading dose, administered on day 1) and 50 mg/m² (maintenance dose, administered once daily) of caspofungin (Merck & Co., Inc.). Therapeutic drug monitoring (TDM) and opportunistic samples were collected as reported previously (9–12). Plasma concentrations of caspofungin were measured with a validated high-performance liquid chromatography-mass spectrometry (HPLC-MS) method, as described previously (1, 13). The calibration curve ranged

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TABLE 1 Baseline characteristics of the 48 children

Parameter ^a	No.	Mean $\pm$ SD	Median (range)
Total patients	48		
Gender (male/female)	28/20		
Condition			
ICU	48		
Regular ward	0		
Age (yr)		6.07 $\pm$ 2.74	5.09 (2.05–11.77)
Current weight (kg)		22.78 $\pm$ 8.71	21.00 (11.80–47.50)
BSA (m ²)		0.84 $\pm$ 0.22	0.79 (0.54–1.39)
Serum creatinine concentration (μ mol/liter)		28.75 $\pm$ 10.15	28.75 (14.00–67.00)
Albumin concentration (g/liter)		33.62 $\pm$ 4.86	33.20 (29.00–49.70)
AST concentration (U/liter)		80.14 $\pm$ 264.44	38.00 (14.00–2198.00)
ALT concentration (U/liter)		84.78 $\pm$ 172.58	45.50 (1.00–1451.00)
Hemoglobin concentration (g/liter)		9.91 $\pm$ 1.55	9.9 (4.70–18.00)
Caspofungin treatment			
Dose (mg/dose)		43.84 $\pm$ 1.22	40.00 (25.00–70.00)
Dose (mg/kg/dose)		2.02 $\pm$ 0.42	1.94 (1.05–3.57)
Dose (mg/m ²)		49.69 $\pm$ 7.18	51.59 (35.96–80.99)

^aICU, intensive care unit; AST, aspartate transaminase; ALT, alanine transaminase.

from 0.25 to 10.0 μ g/ml. The interday and intraday coefficients of variation for controls were 3.0% and 2.0%, respectively. The lower limit of quantification was 0.25 μ g/ml. Nonlinear mixed-effect modeling using a first-order conditional estimation (FOCE) method with interaction was implemented using NONMEM v7.2, PsN v2.30, and NPDE R package v1.2 (14–19). Covariates, i.e., body weight, BSA, age, serum creatinine concentration, and albumin concentration, were investigated to determine the covariate-parameter relationships using the likelihood ratio test. A MIC of 1.0 μ g/ml was utilized for dosing regimen optimization with Monte Carlo simulations (11). BSA regimens were calculated using the Mosteller formula, as follows: $BSA (m^2) = [(height [cm] \times weight [kg])/3,600]^{1/2}$ (20).

In total, 48 patients, 2 to 12 years of age, in the model-building group fulfilled the enrollment criteria and provided informed consent between July 2014 and November 2016. All patients received caspofungin treatment with the maximum loading dose and daily dose not exceeding 70 mg. No patients discontinued caspofungin treatment due to adverse events, and there were no drug-related adverse events associated with caspofungin therapy. The mean $\pm$ standard deviation (SD) BSA of the 48 patients in this study was $0.84 \pm 0.22 m^2$ (range, 0.54 to 1.39 m^2). The detailed characteristics of the participants are summarized in Table 1.

A total of 159 caspofungin plasma samples were collected and analyzed for modeling building. The concentrations of caspofungin in the samples ranged from 0.55 to 31.98 μ g/ml. Compared to the one-compartment model, the objective function value (OFV) and residual variability of the two-compartment model were remarkably decreased, demonstrating that a two-compartment model with first-order elimination best described caspofungin concentration-time data. In addition, a proportional model best described residual variability, rather than an additive or combined additive and proportional error model.

During the forward covariate selection process, BSA, body weight, and age had significant effects on pharmacokinetic parameters, decreasing the OFV by 19.24, 9.55, and 29.11 points, respectively, for clearance (CL). BSA and body weight were defined as important covariates for the volume of distribution in the central compartment (V_1) and the volume of distribution in the peripheral compartment (V_2). The final models were constructed based on a stepwise backward regression. BSA and body weight were incorporated into the structural model in parallel, resulting in remarkable decreases in the OFV of 37.091 and 33.108 points, respectively. The models could not be further improved by including age. Finally, BSA was determined to be a more important covariate than body weight for pharmacokinetics (difference in OFV, 3.84 points;

TABLE 2 Population pharmacokinetic parameters of caspofungin and bootstrap results

Parameter ^a	From full data set		Bootstrap median (95% CI)
	Final estimate	Relative standard error (%)	
CL (liters/h) [$CL = \theta_1 \times F_{BSA-CL} \times \exp(\eta_1)$]	0.165	4.4	0.161 (0.137–0.174)
V_1 (liters) [$V_1 = \theta_2 \times F_{BSA-V1}$]	1.730	8.2	1.910 (1.590–2.605)
Q (liters/h) [$Q = \theta_3 \times \exp(\eta_2)$]	0.351	47.6	0.169 (0.069–0.739)
V_2 (liters) [$V_2 = \theta_4 \times \exp(\eta_3)$]	0.943	22.3	1.500 (0.611–3.520)
$F_{BSA-CL} = (BSA/0.79)^{\theta_5}$	1.300	13.8	1.420 (1.025–1.865)
$F_{BSA-V1} = (BSA/0.79)^{\theta_6}$	1.500	13.5	1.380 (0.907–1.955)
Interindividual variability (%)			
CL	0.242	21.0	0.237 (0.144–0.299)
Q	1.616	90.0	1.086 (0.188–2.500)
V	0.766	71.6	0.828 (0.286–1.979)
Residual variability (%)	0.196	19.6	0.184 (0.153–0.204)

^a Q , intercompartment clearance. In our population, 0.79 m² was the median BSA value. θ_1 , typical value of CL; θ_2 , typical value of V_1 ; θ_3 , typical value of Q ; θ_4 , typical value of V_2 ; θ_5 , typical value of exponent for BSA effect on CL; θ_6 , typical value of exponent for BSA effect on V_1 ; η_i , variance of the interindividual variability of the specified parameter; F_{BSA-CL} , effect of BSA on CL; F_{BSA-V1} , effect of BSA on V_1 .

$P < 0.05$, χ^2 distribution with 1 degree of freedom). The η and ε shrinkage values were 12.064% and 19.38%, respectively, for CL. Detailed parameter estimates for the final pharmacokinetic model are summarized in Table 2. The median CL and V_1 at steady state were 0.21 liters/h/m² (range, 0.05 to 0.38 liters/h/m²) and 2.23 liters/m² (range, 0.29 to 2.91 liters/m²), respectively.

Regarding model validation, goodness-of-fit plots revealed that the final model had satisfactory performance and no significant bias (Fig. 1A and B). There were no trends in the plots of conditional weighted residuals (CWRES) versus time and predicted concentrations versus observed concentrations (Fig. 1C and D). A bootstrap analysis revealed that the median parameter estimates were within the 95% confidence interval (CI), indicating that the final model had good predictive performance and could redetermine the estimates of population pharmacokinetic parameters (Table 2). The normalized prediction distribution errors (NPDEs) are presented in Fig. 1E and F. The mean and variance of the NPDEs were 0.02 and 1.11, respectively.

In this study, we used the published susceptibility breakpoint of 1 μ g/liter as the target MIC to perform a Monte Carlo simulation (3, 11). Our simulation revealed that more than 95% of children (2 to 12 years of age) had caspofungin trough concentrations that exceeded the target MIC of 1 μ g/liter when they were treated with 50 mg/m² caspofungin once a day, with a loading dose of 70 mg/m² on the first day.

Our study compared the effects of the developmental factors (BSA and body weight) on caspofungin pharmacokinetics using population pharmacokinetic simulation methodology. Population pharmacokinetic analysis of caspofungin was performed with real-world data obtained from patients undergoing antifungal treatment. Our preliminary results showed that a two-compartment model with first-order elimination was optimal for data modeling. Various covariates, including BSA, body weight, age, serum creatinine concentration, and albumin concentration were evaluated during model development, and the analyses revealed that BSA had the best fit as a covariate of CL and V_1 for caspofungin pharmacokinetics in this population. This model could not be further improved with any other examined covariates. Compared with BSA, body weight was another covariate found to play a statistically significant role in caspofungin pharmacokinetics, as reported in a study by Stone et al. (8). However, the final model based on body weight as a covariate was not stable enough for use, consistent with previously reported results (4–8). The effect of age was also evaluated via a model-building process. Our results indicated that age did not improve the model, because the pediatric patients enrolled in this study were of one age group and the increase in age was covered by the changes in BSA or body weight. Finally, our model supported a BSA-based dosing regimen, which is in agreement with labeling studies (4, 9). In the study by Walsh et al. (5), 39 children and adolescents were stratified into different

FIG 1 Evaluation of caspofungin models. (A) Population predicted concentrations (PRED) versus observed concentrations (directly visualized [DV]). (B) Individual predicted concentrations (IPRED) versus observed concentrations. (C) CWRES versus time. (D) CWRES versus population predicted concentrations. (E) Quantile-quantile plot of the distribution of NPDEs versus the theoretical $N(0,1)$ distribution. (F) Histogram of the distribution of NPDEs, overlaid with the density of a standard Gaussian distribution.

groups based on the caspofungin dosing regimen, i.e., body weight-based approach or BSA-based approach. Although the study by Walsh et al. (5) included a small number of subjects and a single dosing regimen based on weight, the first evaluation of caspofungin demonstrated that BSA-based dosing of caspofungin was more appropriate than body weight-based scaling, and it provided a basis for future studies with pediatric patients. Our population pharmacokinetic study confirmed that BSA is a more important covariate than weight for pharmacokinetics.

Labeling pharmacokinetic studies are often conducted with selected patients, with restrictive inclusion and exclusion criteria. Indeed, real clinical practice-related and/or disease-related factors cannot be evaluated at this stage. Real-world data in addition to labeling data are necessary to define the optimal pediatric dose. Our study, as a companion to the labeling study, supported an optimal caspofungin dosing regimen

based on the BSA, as calculated with the Mosteller formula, rather than a weight-adjusted strategy.

Analysis of caspofungin treatment of children 2 to 12 years of age with a population pharmacokinetic model revealed that BSA, body weight, and age had significant impacts on the pharmacokinetics. Specifically, a two-compartment model with BSA as a covariate for CL and V_1 best described our data. These results support the conclusion that caspofungin dosages for children 2 to 12 years of age should be based on patient BSA.

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