Dose reduction of caspofungin in ICU patients with Child Pugh B will result in suboptimal exposure

Martial LC(1,2), Brüggemann RJ(1,2), Schouten JA(3), van Leeuwen HJ(4), van Zanten AR(5), de Lange DW(6), Verweij PE(7,2), Pickkers P(8), Muilwijk EW(1,2), Dorlo TPC(9,10).

(1)Department of Pharmacy, Radboud university medical center, Nijmegen, The Netherlands (2) The Netherlands Radboud Institute for Health Sciences, Nijmegen, The Netherlands (3)Department of Intensive Care, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands (4)Department of Intensive Care, Rijnstate Hospital, Arnhem, The Netherlands (5)Department of Intensive Care, Gelderse Vallei Hospital, Ede, The Netherlands (6)Department of Intensive Care and National Poison Information Center, University Medical Center Utrecht, Utrecht, The Netherlands (7) Department of Medical Microbiology, Radboud university medical center, Nijmegen, The Netherlands (8)Department of Intensive Care, Radboud university medical center, Nijmegen, The Netherlands (9)Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden (10) Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht University, Utrecht, the Netherlands.

Background

Caspofungin is an echinocandin antifungal agent used as first-line therapy for the treatment of invasive candidiasis. [1] Caspofungin is administered intravenous at a loading dose of 70mg on day 1, followed by 50mg maintenance QD. Maintenance dose should be increased to 70mg for bodyweight (BW) ≥80kg and decreased to 35mg for patients with Child-Pugh score B (CPB). CPB is a composite score used to assess the prognosis of liver disease. As this classification is only valid for patients with cirrhotic livers, CPB based dose adjustments may result in suboptimal exposure. AUC/MIC has been proposed as the PK-PD target parameter.

The objectives of this work were (i) to evaluate the effect of the typical ICU patient characteristics on the PK properties of caspofungin and **(ii)** to evaluate *in silico* the probability of target attainment in this population following various dosing regimens. The results of a noncompartmental analysis of this study were published previously. [2]

METHODS

Study design and population

- Open-label, multi-centre, multiple dose, observational trial
- ICU patients with suspected/proven fungal infection
- Caspofungin treatment: 70mg loading, 50mg QD maintenance (70mg if bodyweight >80kg, 35 mg if CPB)

Pharmacokinetic sampling

- 2 PK curves on days 3 and 7
- Time points day 3: t=0 (pre-dose) 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 hours post infusion; time points day 7: t=0 (pre-dose), 1, 4, 8, 12, and 24 hours post infusion
- Additional trough samples on all other study days and until 3 days after stopping caspofungin

Population PK modelling

- NONMEM version 7.2 (ICON Development solutions, Ellicott City, MA, USA), Perl-Speaks-NONMEM (version 4.2.0), Xpose (version 4.5.3); Pirana interface
- First order conditional estimation method with interaction

Covariate analysis

- Stepwise covariate modelling (SCM) tested covariates (baseline values) on CL and V
- Continuous covariates: age, BW, length, lean body mass, body mass index, body temperature, serum creatinine, ureum, albumin, liver enzymes, C-reactive protein, blood pH, glomerular filtration rate (GFR); linear, exponential and power conditions
- Categorical covariates: gender, Child-Pugh score and ab-/normal GFR (breakpoint >60 ml/min); linear conditions
- Forward inclusion criterion $p<0.05$ (OFV decrease ≥3.84, χ^2, 1df)
- Backward exclusion criterion $p<0.01$ (OFV increase ≥6.64, χ^2, 1df)
- BW was incorporated a priori on CL (allometrically with a power exponent of 0.75) and on V (power exponent of 1) and standardized to a 70 kg patient [3,4]

Monte Carlo simulations of alternative dosing regimens

Five dosing regimens were simulated in a cohort of 1706 AML/MDS and stem cell transplantation patients (Tables 1 and 2).

Exposure to caspofungin in terms of $AUC_{0\text{-}24h}$ was assessed on day 14 of therapy. Differences in exposure (between treatment days and between BW) were statistically tested with Wilcoxon Rank Sum test.

Table 1 *Demographic characteristics simulation cohort (n=1706).*

	Age	WT	BMI	SEX % female
Median (range)	59.2 (18-81)	76.0 (39-145)	24.7 (13-42)	40%

Table 2 *Dosing regimens for simulations. Regimes I and II are licensed* [1,5].

	Loading dose	Maintenance dose
Regime I	70 mg	BW ≤80 kg: 50 mg BW >80 kg: 70 mg
Regime II	70 mg	35 mg
Regime III	100 mg	70 mg
Regime IV	100 mg	50 mg
Regime V	100 mg	100 mg

Pharmacokinetic target attainment (PTA)

Target attainment based on a preclinical PK target (AUC/MIC≥865 based on –log kill/24 hours) for *C.albicans* was assessed on day 14 for relevant MICs (0.016, 0.03, 0.06, 0.125, 0.5, 1.0). [6]

RESULTS

Patients

- 21 patients (8 female) with a total of 419 PK observations
- Median age 71 years (range 45-80); median BW 75 kg (range 55-99)
- All patients classified with CPB
- CPB was probably driven by their hypoalbuminemia (≤34 g/L)

Pop PK model

A two-compartment disposition model with first-order elimination from the central compartment and a combined proportional and additive residual error model fitted the data best. An OMEGA covariance block (CL&V1) further improved the model (dOFV=-8.6). SCM could not identify any covariates significantly associated with CL and V1. Parameter estimates with bootstrap derived precisions of the final model are shown in Table 3. Basic GOF plots are shown in Figure 1 and the VPC of the final model is shown in Figure 2. Numerical predictive checks showed that 1.4% (95%CI 0-7.9%) of observations fell below 95%PI and 5.0% (0-8.4%) fell above 95%PI.

Table 3 *Parameter estimates of the final model of caspofungin in ICU patients*

	Parameter estimates [RSE] (Shrinkage)	Bootstrap parameter estimates (n=904/1000) Mean (95%CI) [RSE]
CL (L/h)	0.55 [7%]	0.55 (0.49-0.61) [6.6%]
V1 (L)	8.93 [8%]	8.98 (8.08-10.10) [7.0%]
Q (L/h)	0.707 [3%]	0.70 (0.50-0.86) [17.1%]
V2 (L)	4.98 [17%]	4.99 (3.71-6.41) [16.7%]
IIV CL (CV%)	30.7 [31%] (0%)	29.4 (21.0-36.8) [31.0%]
IIV V1 (CV%)	25.6 [51%] (6%)	25.5 (15.1-35.4) [48.7%]
IIV Q	0 FIX	0 FIX
IIV V2 (CV%)	75.8 [65%] (16%)	73.4 (21.6-128.8) [71.7%]
Proportional residual error	0.148 (17%)	0.147 (0.131-0.163) [6.8%]
Additional residual error	Fix 0.01	

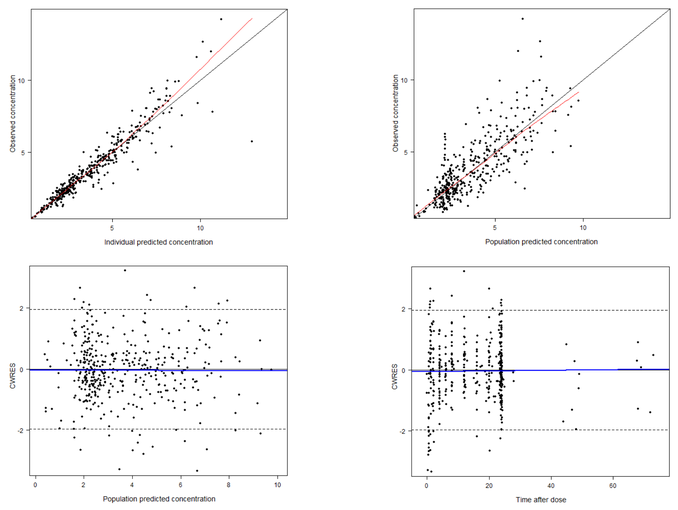

Figure 1 *Goodness-of-fit plots for the final PK model of caspofungin. CWRES= conditional weighted residuals The thin black lines indicate unit line or the line of identity. The thick lines (red or blue) are smooth lines showing the trend in the observations.*

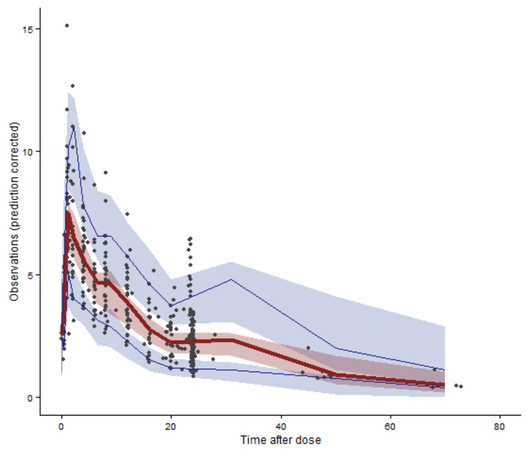

Figure 2 *Visual predictive check for the final PK model of caspofungin, based on n=1000 simulations. Prediction-corrected simulated (areas) and observed (circles and lines) caspofungin concentrations versus time after dose (hours). The thick red line connects the observed median values per bin. The solid thinner blue lines connect the 5th and 95th percentiles of the observations. The blue areas are te 95% CI of the 5th and 95th percentiles. The red area indicates the CI of the median.*

References
[1] Pappas et al. Clin Infect Dis 2009; 48(5):503-35
[2] Muilwijk et al. JAC 2014; 69(12):3294-9
[3] Wurthwein et al. AAC 2013; 57(4):1664-71
[4] Hall et al. AAC 2013; 57(5):2259-64
[5] European Medicines agency; Cancidas EPAR; 26-09-2014;http://www.ema.europa.Eu/docs/en_GB/document_library/EPAR_Product_Information/human/000379/WC500021033.pdf
[6] Andes et al. AAC 2010; 54(6):2497-506

RESULTS (CONTINUED)

Monte Carlo simulations of alternative dosing regimens

Daily exposure ($AUC_{0\text{-}24h}$) on days 14 achieved by different dosing regimens is shown in Figure 3. >75% of patients on regimen II (35 mg maintenance) showed an $AUC_{0\text{-}24h}$ lower than 100 (median $AUC_{0\text{-}24h}$ for healthy volunteers). $AUC_{0\text{-}24h}$ were significantly different between all treatment regimens. Also, higher body weight (BW>80kg) resulted in significant lower exposure than lower bodyweight (BW≤80kg) ($p<0.01$). Concentration time curves are shown in Figure 4. Higher loading dose resulted in higher earlier exposure (reg III-V).

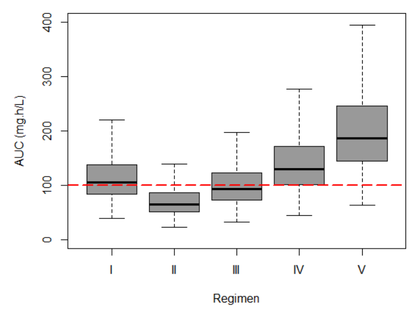

Figure 3 *$AUC_{0\text{-}24h}$ on day 14 for the whole cohort, irrespective of bodyweight. Red line represents $AUC_{0\text{-}24h}$ for healthy volunteers. (I) 70mg loading dose with 50mg maintenance in patients with BW≤80 kg or with 70mg maintenance in patients with BW>80 kg; (II) 70mg loading dose followed by 35mg; (III) 100mg loading dose with 50mg maintenance; (IV) 100mg loading dose with 70mg maintenance and (V) a 100mg loading dose with 100mg maintenance.*

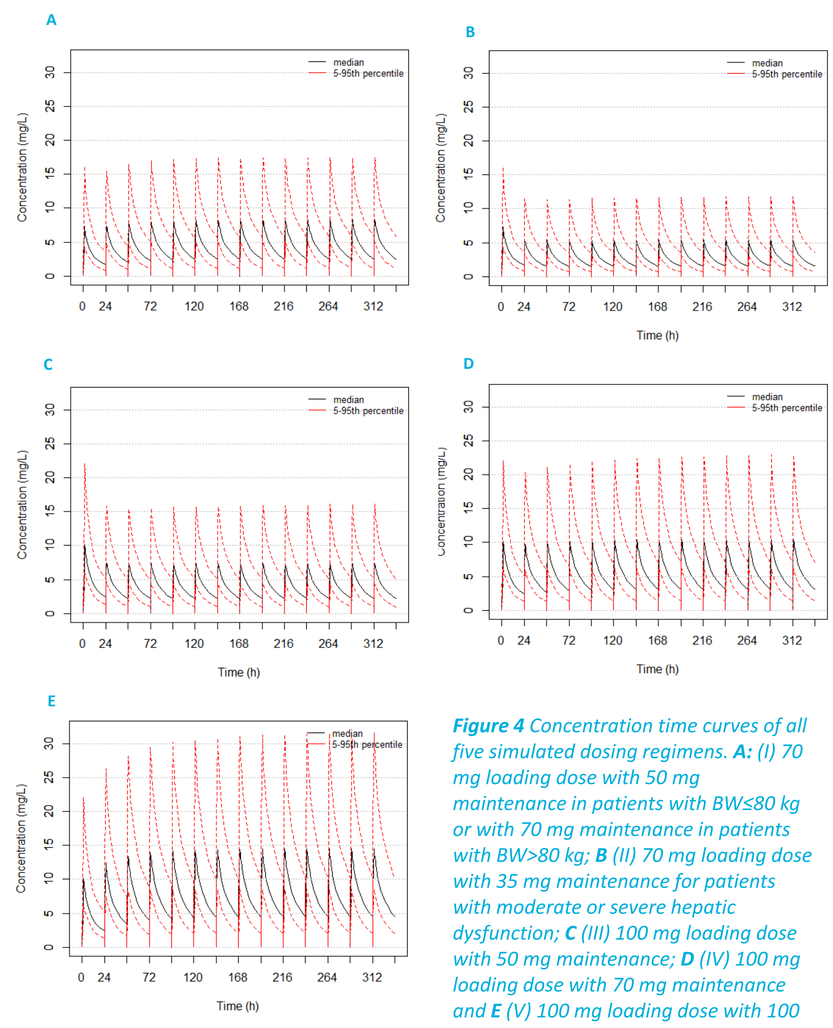

Figure 4 *Concentration time curves of all five simulated dosing regimens. **A:** (I) 70 mg loading dose with 50 mg maintenance in patients with BW≤80 kg or with 70 mg maintenance in patients with BW>80 kg; **B** (II) 70 mg loading dose with 35 mg maintenance for patients with moderate or severe hepatic dysfunction; **C** (III) 100 mg loading dose with 50 mg maintenance; **D** (IV) 100 mg loading dose with 70 mg maintenance and **E** (V) 100 mg loading dose with 100 mg maintenance.*

Pharmacokinetic target attainment (PTA)

Target attainment based on a simulated cohort (n=1706) patients on five regimens and for different MIC values is shown in Figure 5. Higher body weight (BW>80kg) resulted in significant lower target attainment than lower body weight (BW≤80kg) (not shown). With an MIC≥0.5 µg/mL none of the regimens resulted in target attainment.

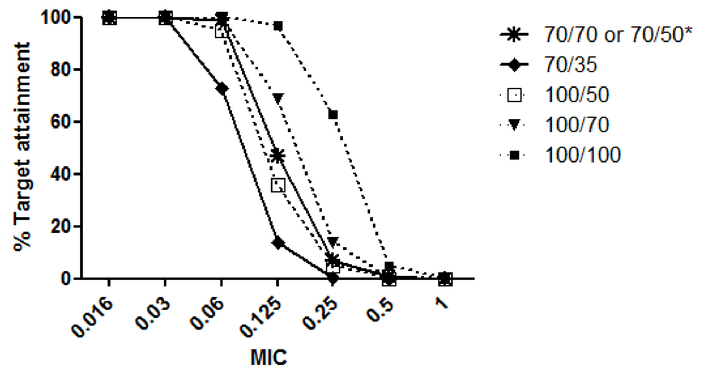

Figure 5 *Target attainment versus MIC for all five simulated regimens based on a preclinical target AUC/MIC ratio of >865. *Regimen is based on BW.*

CONCLUSIONS

- Caspofungin maintenance should not be reduced in non-cirrhotic patients with CPB score
- A higher loading dose is to be recommended to early attain target concentrations
- PTA is higher if maintenance dose is increased to 70 mg

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Lisa Martial, Radboud university medial center
E-mail: lisa.martiall@radboudumc.nll