

Population Pharmacokinetics of Caspofungin in a Phase II Dose Escalation Study

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OBJECTIVE

Caspofungin (CAS) is used for management of proven or probable invasive fungal infections. At present, CAS is recommended at 50 mg once daily (QD), maximum loading and daily maintenance dose should not exceed 70 mg. Preclinical and limited clinical data support the concept of dose-dependent antifungal efficacy of CAS. In a multicenter phase II dose escalation study, safety, tolerability and population pharmacokinetics (PopPK) of CAS doses up to 200 mg QD were studied.

METHODS

Fourty-six patients under immunocompromising condition with proven or probable invasive aspergillosis were included in the PopPK analysis. CAS was administered as 2h infusion at doses of 70, 100, 150 and 200 mg QD, resp.. CAS pharmacokinetic (PK) sampling (n=468 samples) was collected on day 1 and at peak and trough time points at days 4, 7, 14, and 28 (70 mg: 9, 100 mg: 8, 50 mg: 9, 200 mg: 20 patients). Concentrations were measured by the LC-MS/MS method. Trough levels were analysed exploratively. PopPK analysis was performed using NONMEM® 7.1.0 and Pirana 2.4.0. For model evaluation, Bootstrap analysis, visual predictive check (VPC) of dose normalised data as well as standardised VPC (SVPC) were performed. As potential covariates on the PK of CAS, dose level, sex, weight (linear; allometric, groups ≤ 80 vs. > 80 kg), age (linear; groups ≤ 65 vs. > 65 years), bilirubin and creatinine clearance were investigated (stepwise inclusion: 0.05 %, backward exclusion: 0.01 %).

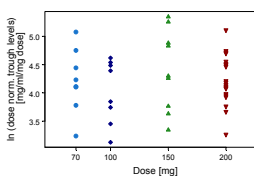
RESULTS

	Number or median (range)				
	70 mg	100 mg	150 mg	200 mg	total
Sex [male / female]	2 / 7	5 / 3	4 / 5	10 / 10	21 / 25
Age [years]	56 (33 - 71)	63 (18 - 71)	61 (38 - 73)	63 (24 - 74)	61 (18 - 74)
Age [≤ 65 , > 65 years]					28 / 18
Body weight [kg]	75 (54 - 94)	78 (61 - 89)	79 (62 - 90)	76 (43 - 104)	76 (43 - 104)
Body weight [≤ 80 , > 80 kg]					32 / 14
Bilirubin day 1 [mg/dl]	0.85 (0.4 - 2.0)	0.8 (0.4 - 2.3)	0.6 (0.3 - 1.3)	0.8 (0.3 - 1.4)	0.8 (0.3 - 2.3)
Crea.CL ⁽¹⁾ day 1 [ml/min]	89 (56 - 174)	117 (82 - 200)	93 (42 - 134)	89 (39 - 260)	102 (39 - 260)
Number PK-samples	96	80	94	198	468

⁽¹⁾ Crea.CL: creatinine clearance

Demographic characteristics did not significantly differ between dose levels.

➤ Trough levels

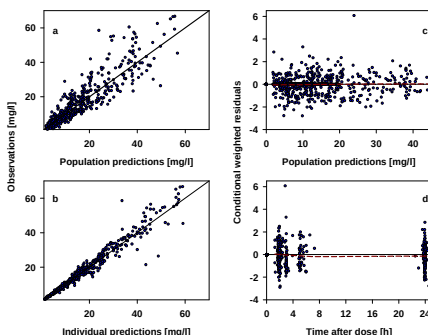


There was no difference of ln-transformed, dose-normalised trough levels of CAS between dose-levels (ANOVA, $p=0.5627$).

➤ Population pharmacokinetics (PopPK)

The PopPK of CAS were best described by a linear two-compartment model with IIV on CL, V1, and V2, covariance between CL and V1 and a proportional error model. During initial covariate selection, sex as covariate on V1, creatinine clearance as covariate on CL, and age as covariate on CL and V1, resp., improved the model. However, the relative standard error of the parameters estimates were unacceptable high, IIV and IOV were not reduced and emirical bayes estimates vs. covariate plots did not improve (η -shrinkage of PK model without covariates: IIV of CL: 3.8 %, IIV of V1: 2.9 %). Therefore, these covariates were not included in further covariate testing. Linear modeling of body weight as covariate on CL and V1 was superior to allometric scaling and was included in the final PopPK model. It is noteworthy, that dose level as potential covariate did not improve the PopPK model.

➤ Final model



Final PopPK model for CAS: Fig. a+b: Observed vs. predicted concentrations. Predictions are made based on population (a) or individual (b) parameters. The line of identity is shown (ϵ -shrinkage: 22 %).

Fig. c+d: CWRES vs. population predictions (c) and time after dose (d), resp..

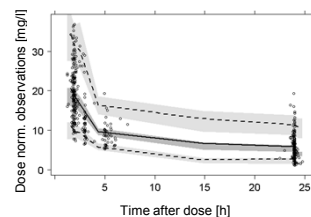
Model parameters		Base Model	Final Model	Bootstrap (N=1776 replicates out of 2000)	
		Estimate (RSE)	Estimate (RSE)	Mean (RSE)	95 % conf. Interval
CL ⁽¹⁾	[l/h]	0.403 (5)	0.411 (5)	0.413 (5)	(0.372 - 0.457)
V1 ⁽¹⁾	[l]	5.73 (5)	5.85 (4)	5.78 (5)	(5.19 - 6.35)
Q	[l/h]	0.844 (14)	0.843 (13)	0.917 (21)	(0.683 - 1.27)
V2	[l]	6.53 (15)	6.53 (15)	6.48 (15)	(4.66 - 8.59)
BW ⁽²⁾ on CL, V1			0.0102 (20)	0.0102 (25)	(0.0049 - 0.0147)
Prop. error [%]		14.3 (10)	14.3 (10)	14.1 (11)	(11.3 - 17.1)
IIV CL [%]		31.4 (10)	28.5 (11)	27.8 (11)	(21.1 - 33.9)
IIV V1 [%]		32.2 (9)	28.8 (10)	28.3 (10)	(22.3 - 33.7)
IIV V2 [%]		66.7 (20)	66.8 (20)	67.5 (21)	(34.2 - 94.7)
IOV CL [%]		16.1 (12)	16.0 (13)	15.9 (13)	(11.2 - 19.5)
Correlation _{CL-V1}		0.842	0.802	0.806	(0.767 - 0.844)

⁽¹⁾ assuming median body weight of 76 kg, ⁽²⁾ BW: body weight

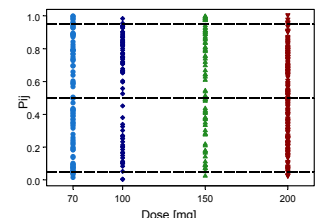
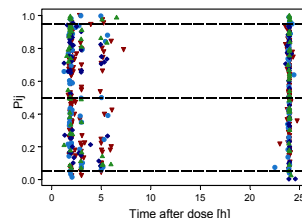
Base model: without covariates, final model: body weight as covariate on CL and V1

All PK parameters were estimated with high precision (RSE ≤ 20 %). The population estimates for the final model were very similar to the mean of the 1776 bootstrap replicates and within the 95 % confidence intervals obtained from the bootstrap analysis.

➤ Simulation based internal model evaluation



VPC: Visual predictive check of dose normalised observations (points) of the final population model. The median (solid line) and the 5th and 95th percentiles (dashed lines) for the dose normalised observations with 95 % confidence inter-vals (gray fields) based on simulations are shown.



SVPC: Standardised visual predictive check:

left panel: Pij as function of time after dose,

right panel: Pij stratified by dose level

VPC of dose-normalised data as well as SVPC confirm the adequacy of the model to describe the data. The even distribution of Pij at the different dose levels further confirms the linear PK of CAS in the examined dose range.

CONCLUSIONS

- CAS showed linear pharmacokinetics across the investigated dose range of 70 to 200 mg QD
- The PopPK were best described by a two compartment model with body weight as covariate on CL and V1
- AUC for patients with body weight of 80 kg is 20 % lower compared to patients with body weight of 60 kg; results are in good agreement with data after standard doses of 50 mg QD (AUC-decrease: 23 %)¹
- The fact, that no PK samples were taken in the time interval of 7.5 and 22 h after dose, might contribute to the high IIV of V2 (67 %)
- Drug exposure at 100 mg QD CAS in the present population were slightly higher (7 %, clinically not relevant) compared to data in healthy adult².

Literature

- EMA, Cancidas, EPAR Product Information, last update: 28.09.2011, (08.05.2012) http://www.emea.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000379/WC500021033.pdf
- Migoya, E. et al. Safety and Pharmacokinetics of Higher Doses of Caspofungin in Healthy Adult Participants. *J. Clin. Pharmacol.* (2010).