Population Pharmacokinetics of Liposomal Amphotericin B, Caspofungin and the Combination of Both in Allogeneic Hematopoietic Stem Cell Recipients

G. Würthwein (1), C. Young (1), C. Lanvers-Kaminsky (2),
G. Silling (3), G. Hempel (2,4), J. Boos (2), A. H. Groll (2)

(1) Centre for clinical trials, University Hospital Münster, Münster, Germany; (2) Department of Paediatric Haematology and Oncology, University Hospital Münster, Münster, Germany; (3) Dept. of Internal Medicine A, Hematology and Oncology, University Hospital Muenster, Muenster, Germany; (4) Department of Pharmaceutical and Medical Chemistry, Clinical Pharmacy, University of Münster, Münster, Germany

OBJECTIVE

Caspofungin (CAS), liposomal amphotericin B (LAMB) and the combination of both (CAS+LAMB) are used for management of invasive fungal infections in allogeneic hematopoietic stem cell (aHSCT) recipients. Little is known, however, about the disposition of both agents and their combination in this special population.

METHODS

The population pharmacokinetics and interactions of CAS and LAMB were investigated within a risk-stratified, randomized, multicenter phase II trial in 53 adult, cyclosporine-immunosuppressed aHSCT patients in the setting of granulocytopenia and refractory fever. Patients received either CAS (50 mg QD; d 1:70 mg,1h infusion), LAMB (3 mg/kg QD, 1h infusion) or the combination of both until defervescence and granulocyte recovery. Pharmacokinetic sampling was mainly performed on days 1 and 4 and thereafter at single time points twice weekly. Concentrations were measured by validated HPLC methods (limit of quantification: CAS: 0.15 mg/L, amphotericin B; 0.1 mg/L).
Data were analyzed NONMEM 6 (FO) and Xpose 3.1.
As potential covariates on the pharmacokinetics of CAS or LAMB comedication (CAS: comedication of LAMB, LAMB: comedication of CAS), sex, weight and BSA were investigated. For bilirubin and creatinine clearance values on day 1 as well as a linear function between all values were tested as covariates. The influence of a single patient on the covariate effect was investigated by plots of Cook's distances. During model building process as well as for covariate selection p<0.001 was used as selection criteria. In order to verify that the model predicts both the central tendency and the variability in the observed data, a visual predictive check was employed.

RESULTS

	CAS [n=19]	LAMB [n=17]	CAS + LAMB [n=17]
	Number or median (range)		
Sex [male / female]	11 / 8	11 / 6	10 / 7
Age [years]	43.4 (20.1, 57.6)	38.9 (18.2, 59.5)	47.9 (20.1, 61.4)
Weight [kg]	79.5 (53.6, 99.1)	72.3 (44.0, 105.3)	79.5 (53.6, 99.1)
BSA [m^2]	1.84 (1.61, 2.21)	1.90 (1.37, 2.35)	1.92 (1.56, 2.24)
Bilirubin day 1 [mg/dL]	1.1 (0.3, 5.1)	1.1 (0.4, 4.9)	1.2 (0.4, 2.5)
day 4 [mg/dL]	1.0 (0.2, 4.9)	1.0 (0.4, 4.8)	1.2 (0.5, 3.7)
Crea. CL day 1 [mL/min]	125 (73.4, 350)	146 (67.9, 250)	136 (91.8, 189)
day 4 [mL/min]	131.9 (90.0, 225)	111 (61.8, 235)	116.9 (83.9, 239)
Number of infusions / pharmacokinetic samples	239 / 239	164 / 182	CAS 242 / 219 LAMB: 236 / 223

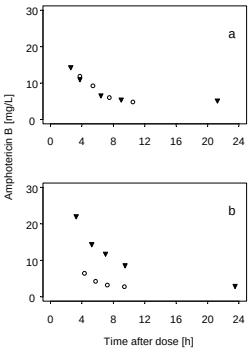
Demographic data as well as covariates on day 1 were comparable in the different treatment arms; there was no significant change of covariates during treatment (except: clearinine clearance after LAMB administration, paired t-Test, p<0.05).
For CAS as well as for LAMB, a deep compartment with a long terminal half-life of about 50 h and 150 h, resp. is reported in literature. However, only 11 and 12 samples, resp. with time after dose greater than 30 h were collected. As the number of data points is too small to model such a compartment, these samples were excluded from further analysis.

➢ PK of CASPOFUNGIN (CAS)

Patients received 5 to 28 (median: 13) CAS-infusions according to protocol (dose: 70 mg on day 1, followed by 50 mg QD; only one dose reduction was performed (35 mg CAS on day 12).
The population pharmacokinetics were best described by a linear two-compartment model with IIV on CL and V1 and a proportional error model.
No one of the tested covariates improved the model on the 0.1 % level; in particular, neither weight nor comedication of LAMB influenced the pharmacokinetics of CAS (decrease in objective function value (OFV) with weight as covariate on CL: -2.925, as covariate on V1: -0.916; increase in OFV with allometric scaling of weight: +18.759; decrease in OFV with comedication as covariate on CL: -0.720, as covariate on V1: -0.155).

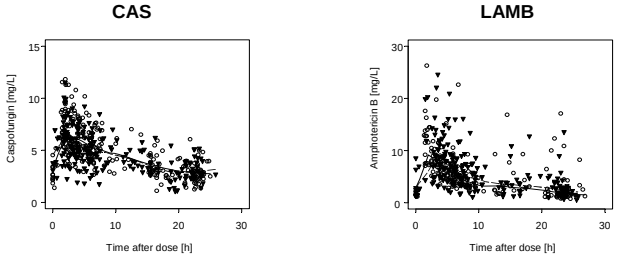
➢ PK of LIPOSOMAL AMPHOTERICIN B (LAMB)

Patients received 4 to 28 (median: 10) LAMB-infusions according to the protocol (LAMB dose: 135 mg to 300 mg (median: 234 mg); LAMB dose: 2.67 mg/kg to 3.46 mg/kg (median: 3.0 mg/kg).
The population pharmacokinetics of LAMB were best described by a linear two-compartment model with IIV on CL, V1, Q and V2 and a combined error model. Neither three-compartment-model nor Michaelis-Menten pharmacokinetics or modeling of time-dependent pharmacokinetics further improved the model.



LAMB: observed plasma concentrations as a function of time after dose for patient a and patient b; open circle: day 1, black triangle: day 4

Weight and bilirubin as covariates on CL improved the model only on the 1 %-level. A significant improvement of OFV was found when baseline creatinine-clearance was included as covariate on CL; the influence was no more significant after omission of one suspected influential patient. Creatinine-clearance as covariate on V1 improved the model on the 0.1 %-level; however, as the inclusion of this covariate did not reduce the IIV of the pharmacokinetic parameters, this covariate was not included in the final pharmacokinetic model. Comedication of CAS did not influence the pharmacokinetics of LAMB (decrease in OFV with CAS-comedication as covariate on CL: -0.005, as covariate on V1: -2.167).
In accordance with data reported in literature, pharmacokinetic parameters showed high interindividual variability.



Observed plasma concentrations as a function of time after dose (open circle and solid curve : CAS- or LAMB, resp.; black triangle and broken curve : CAS+LAMB).

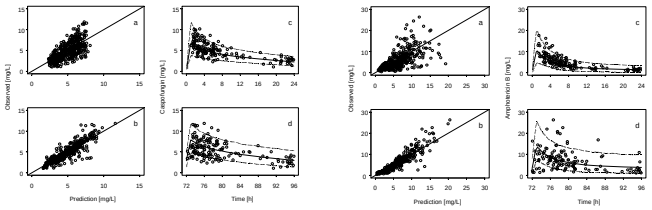


Fig. a+b: Observed vs predicted concentrations. Predictions are made based on population (a) or individual (b) parameters. The line y=x is the line of identity.
Fig. c+d: Visual predictive check of the final population models: Plots are shown for plasma CAS or amphotericin B-concentrations on day 1 (c) and day 4 (d), resp., vs time after first dose. The population-predicted profile (50th percentile) is shown by the solid line, and the 90 % prediction intervals are encompassed by the broken lines in each plot.

➢ FINAL MODELS

		CAS Estimate	(SE)	IIV		LAMB Estimate	(SE)	IIV	
CL	[L/h]	0.426	(5.2)	24	(22)	0.786	(24)	69	(48)
V1	[L]	9.25	(8.3)	29	(40)	18.6	(13)	42	(41)
Q	[L/h]	0.823	(37)			2.86	(30)	56	(75)
V2	[L]	3.06	(17)			81.7	(31)	60	(53)
Prop. error	[%]	20	(20)			24	(25)		
Additive error	[mg/L]					1.91	(38)		

CONCLUSIONS

- For CAS as well as for LAMB the population-pharmacokinetics were best described by two compartment models.
- As compared to published data, drug exposure to CAS was slightly higher (clinically not relevant), which may be explained by the comedication with cyclosporine A.
- For CAS, in contrast to the FDA label information, the EPAR for Cancidas® (active substance caspofungin) recommends dose adjustment for patients over 80 kg. Although 15 of 36 patients having a body weight over 80 kg, the present population does not support the need of dose adjustment according to weight.
- In accordance with data in literature, LAMB pharmacokinetics are characterized by significant interpatient variability.
- Drug exposure of LAMB was comparable to other populations.
- The pharmacokinetics of CAS were not altered by the coadministration of LAMB and, similarly, the pharmacokinetics of LAMB were not altered by coadministration of CAS.