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A Population Pharmacokinetic Model Describing the Activity-Time-Course of PEG-Asparaginase in Children

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Objective

Asparaginase is an important part of induction therapy in the treatment of acute lymphoblstic leukaemia (ALL) removing asparagine from plasma. Drug monitoring of plasma asparaginase activity is done by measuring the enzyme activity in the german ALL-BFM 1995 study. First-order kinetics [1] and Michaelis-Menten models [2] were suggested to describe the pharmacokinetics. However, all the models are not predictive. Therefore, we retrospectively analysed data from ALL-BFM 95 patients with the aim to:

- develop a model describing the pharmacokinetics in all dosing levels
- analyse the influence of covariates
- identify optimal time points for blood sampling
- provide a rationale for dose recommendation

Patients and Methods

- 185 patients with ALL or NHL (96 female, 87 male)
- dose: between 500 and 2500 U/m² administered i.v.
- activity quantified using an activity assay with a LOQ of 2.5 U/l[3]
- 1189 serum activity measurements from 238 administrations
- age, weight, height, body surface area documented

	Age [years]	Height [m]	Weight [kg]	BSA [m²]
Median	6	1.21	23.8	0.93
Min	0.8	0.69	8.7	0.4
Max	19	1.92	106	2.23

Tab. 1: Patient characteristics

Data analysis:

- NONMEM Vers. V, FO method
- proportional and combined proportional and additive error models

Results

A first-order one compartment model did not describe the fast decline in the plasma concentrations sufficiently (Tab. 2, Fig.1a). Michaelis-Menten models gave a better fit. However, inconsistent results were obtained when different dosing levels were analysed together. Polynomial models also gave no improvements of the fit.

Model description	objective function	V [l/m²]	ω(V)	Cl [l day⁻¹ m²]	ω(Cl)	residual error
1-compartment-model	13601	1.31	0.61	0.104	0.291	36%
2-compartment-model	13863	0.04, V_2 1.24		0.09	0.837	37%
Michaelis-Menten-Model	13643	0.886	0.124	Vmax 788, Km 9530		23%
2nd order polynomial	14466	1.39	0.08	F1= 0.227	0.11	36%
1-compartment-models:						
Cl=..$e^{x*BSA-Dosis}$	13534	1.26	0.56	0.0784	0.256	34%
Cl=..e^{x*TAD}	13188	1.16	0.198	0.0578	0.437	30%
Cl=..$e^{0.0853*TAD}$, IOV on Cl, V	12635	1.05	0.0749	0.0603	0.502	4.12%, 16.4 U/l

Tab. 2: Model development

The best results were obtained with increasing clearance after administration according to the formula:

$$Cl = \theta_1 \cdot e^{0.0853 \cdot t} + IOV + \eta_1$$

with Cl: clearance, θ: population mean, t: time from the start of infusion IOV: interoccasion variability, η: interindividual variability. As can be seen from Fig.1b, the model describes the decline in the plasma activity sufficiently. The parameters are shown in Tab. 3.

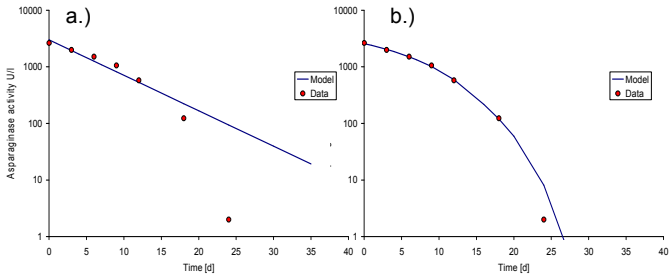

Fig. 1: Individual model predictions and measured activity for a patient receiving 2500 U/m². a.) One compartment model, b.) final model.

Parameter	population mean	interindividual variability	intraindividual variability
$Cl_{initial}$ [ml day⁻¹ m⁻²]	60.3	71%	63%
V [l m⁻²]	1.05	27%	21%
residual error proportional	4.12%		
residual error additive [U/l]	16.4		

Tab. 3: Final parameter estimates

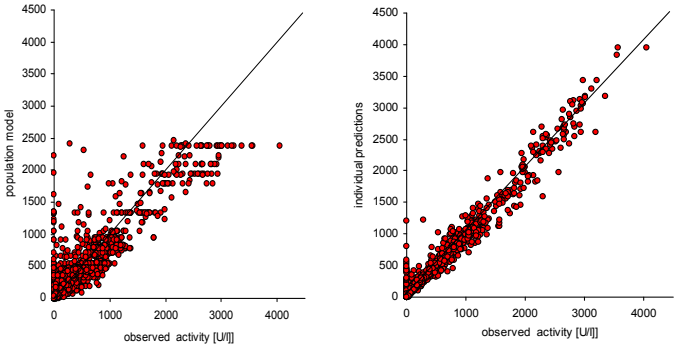

Fig. 2: Goodness of fit plots of the final model for the population predictions (left) and the individual predictions (right)

The model fits the data sufficiently for most patients (Fig. 2) and can predict the plasma activity for all dosing groups. With the clearance increasing with time low activity levels are reached after about 28 days in all of the patients regardless of the administrated dose.

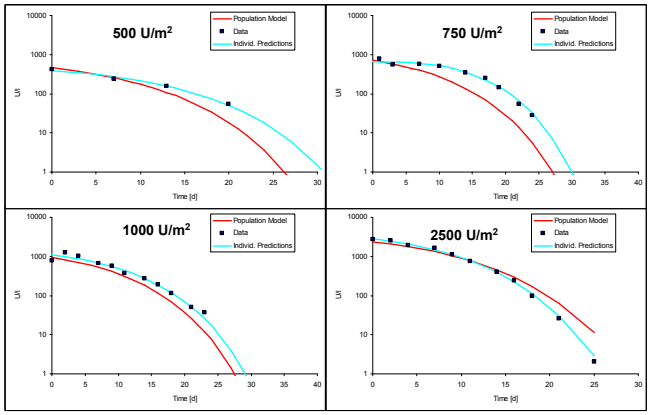

Fig. 3: Population model, individual prediction and measured asparaginase serum activity at different dosing levels.

A subgroup of patients displays a very fast decline in the asparaginase plasma activity. This is represented by the clearance estimates of the model shown in Fig. 4. About one third of the patients have a very high clearance displaying silent inactivation due to the formation of antibodies towards asparaginase.

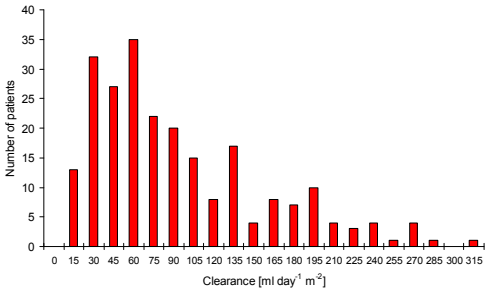

Fig. 4: Histogram of the parameter estimates of the initial clearance.

Conclusion

- The model describes the activity-time course in plasma sufficiently and is applicable for all dosing groups available.
- Body surface area is the best predictor for clearance and volume of distribution.
- 33% of the patients show a higher clearance resulting in a fast decline of the plasma activity.
- Validation of the model will be done using data from the subsequent ALL trial.

References:

1. Avramis VI et al. Blood 2002, 99: 1986-94.
2. Mueller HJ et al. Cancer Chemother Pharmacol 2002, 49: 149-154
3. Lanvers C et al. Anal Biochem 2002, 309: 117-126 .