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A preliminary population pharmacokinetic model for dose selection of treosulfan used in conditioning treatment prior to haematopoietic stem cell transplantation (HSCT) in children

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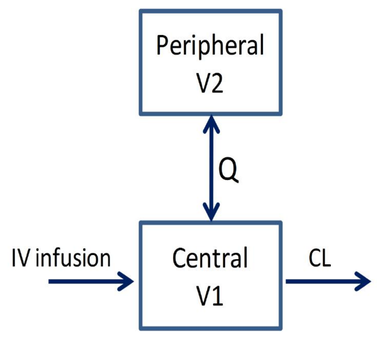
Introduction

Treosulfan, an alkylating agent, is currently being developed by medac as a component of a conditioning regimen prior to HSCT in adults and children. Within a paediatric investigational plan (PIP) agreed by the Paediatric Committee of the European Medicines Agency, a population pharmacokinetic (PopPK) model had to be developed to select dosages for the agreed studies in paediatric patients from 1 month to 18 years of age.

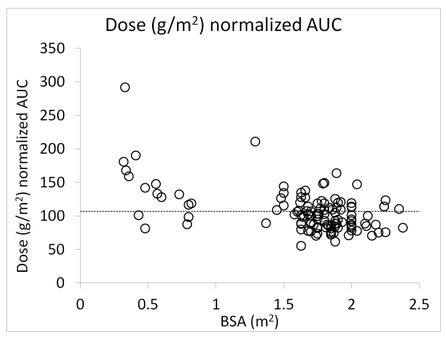
PK model

The preliminary PopPK model for treosulfan consisted of two compartments with a first order distribution and elimination processes.



V1: Volume of distribution of central compartment (L)
CL: Clearance (L/h)
V2: Volume of distribution of peripheral compartment (L)
Q: Inter-compartmental clearance (L/h)

Treosulfan AUC *vs* BSA



When the administered doses were calculated in g/m^2, the exposure to treosulfan (area under the curve, AUC) was significantly increased in children, compared to adults. Targeting for equal exposure in children implies the dose should be adapted in children.

Results

A covariate analysis revealed that body surface area (BSA) was the only relevant covariate for clearance and volumes of distribution.

Based on the estimated PopPK model, the functional relationship between clearance and BSA was derived:

$$\text{DOSE}_{\text{model}}\,(\text{g}) = \frac{\text{Target AUC}\,(\mu\text{g.h/mL})}{1000} \times 17.8 \times \left(\frac{\text{BSA}}{1.75}\right)^{1.29}$$

For the planned paediatric studies the dose resulting in similar exposure as the effective exposure in adults was calculated based on above equation.

For feasibility purposes, a simplified scheme of treosulfan dosing was deduced thereof:

BSA	Daily Treosulfan Dose
≤ 0.5 m^2	10 g/m^2
> 0.5 – 1 m^2	12 g/m^2
> 1.0 m^2	14 g/m^2

Materials and Methods

All available treosulfan pharmacokinetic data from 7 clinical studies consisting of data from 93 adults and 23 children (0.4 – 17 years) were used to develop a PopPK model for treosulfan using NONMEM and to investigate the potential influence of 6 covariates on treosulfan exposure (i.e. body surface area [BSA], age, body weight, height, renal function and use of diuretics).

Paediatric dose selection was aimed to target a similar exposure in children as obtained in adults after intravenous administration of the clinically effective dose of 14 g/m^2/day treosulfan for 3 consecutive days for conditioning prior HSCT.

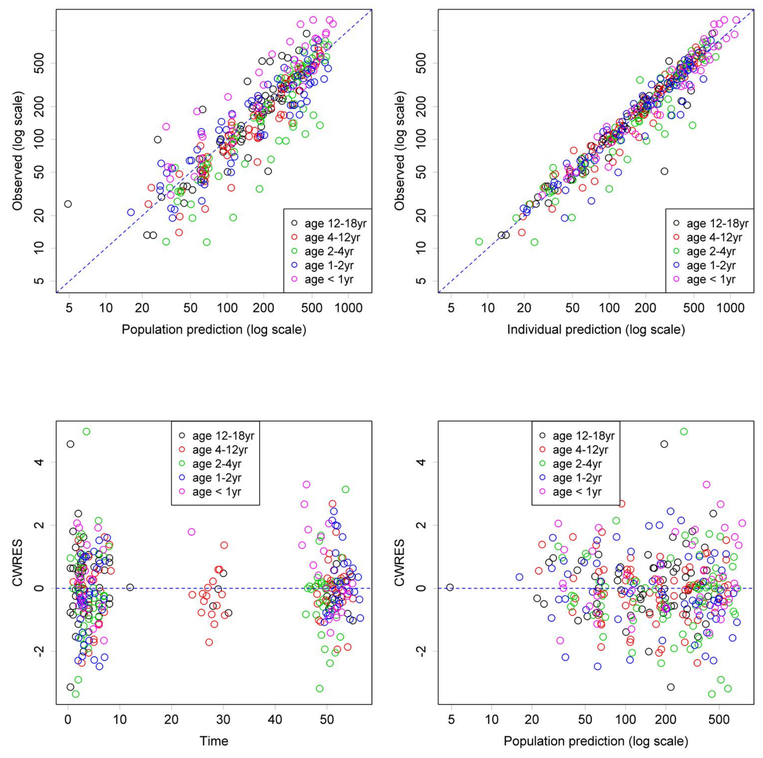
Non-linear mixed effects modeling was performed using NONMEM (v7.1, Method FOCE INTER) with gfortran (v4.5.0) together with PSN (v3.4.2) and R (v2.11.1).

Conclusion

The PopPK model for treosulfan is robust and accurately predicted exposure in children older than 1 year of age. For infants a best estimate could be given only as the dataset merely included limited data of children below 1 year of age. The planned paediatric transplant trials will start with the deflected dosing table and will update the PopPK model accordingly to further investigate its validity in children with malignant or non-malignant diseases qualifying for HSCT.

Goodness-of-Fit Plots

The PopPK model provided an adequate fit to the data and model diagnostics revealed no significant bias although the diagnostic plots of observed vs population predicted concentrations indicate a slight underestimation for age group <1 year. Therefore, the PopPK model will be updated with new data from the upcoming paediatric trials in children with malignant or non-malignant diseases qualifying for HSCT to further investigate its validity, especially for the age group <1 year.



Parameter Table

Parameter	Estimate	CV[%]	95% CI **	
			Lower	Upper
V1*	16.8	11.6	12.7	20.5
CL*	17.8	2.43	16.9	18.5
V2*	22.1	7.34	18.6	25.1
Q	31.2	15.6	22.2	42.8
β(BSA,V2)	1.24	7.49	1.05	1.47
β(BSA,CL)	1.29	4.99	1.16	1.41
β(BSA,V1)	2.05	10.1	1.56	2.66
Ω(V1)	0.143	28.4	0.0686	0.237
Ω(CL)	0.0535	17.5	0.0352	0.0719
Ω(V2)	0.0514	32.0	0.0115	0.0801
Ω(Q)	0.245	38.9	0.0506	0.463
σ1	0.0463	12.5	0.0337	0.0581
σ2	6.53	78.8	1.17	33.1

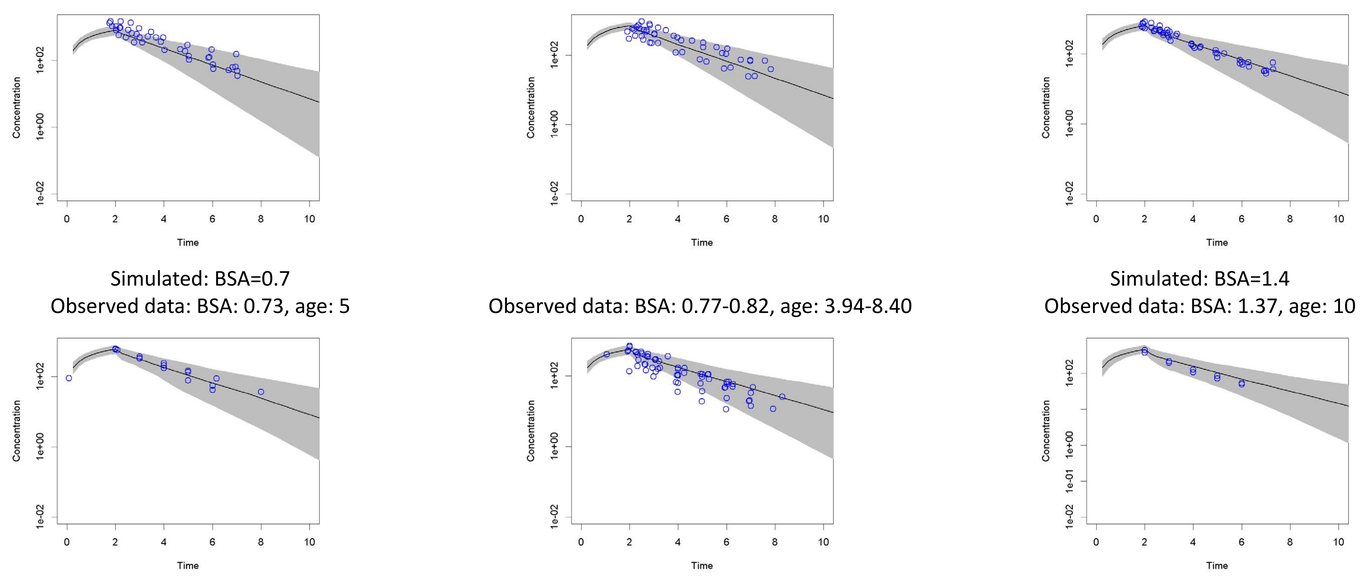
* Value for a typical subject with BSA of 1.75m^2
** based on 990 successful bootstrap runs.
B denotes the allometric coefficient of the covariate for the model parameter
Ω denotes the variance of the inter individual variability on the model parameter
σ1 denotes the variance of the constant CV residual error
σ2 denotes the variance of the additive residual error

Visual predictive checks

Simulated: BSA=0.3
Observed data: BSA: 0.32-0.34, age: 0.40-0.69

Simulated: BSA=0.4
Observed data: BSA: 0.36-0.43, age: 1.26-1.48

Simulated: BSA=0.6
Observed data: BSA: 0.56-0.60, age: 2.69-3.23



Simulated: BSA=0.7
Observed data: BSA: 0.73, age: 5

Simulated: BSA=0.77-0.82, age: 3.94-8.40

Simulated: BSA=1.4
Observed data: BSA: 1.37, age: 10

Grey shaded bands indicate concentration regions in which 95% of the simulated concentration values are contained. Solid lines indicate calculated medians, and circles display measured concentration values. The simulated infusion duration was 2 hours. The actual infusion duration ranged between 1.7 and 2.8 hours, instead of the simulated 2.0 hours. In addition, individual BSA deviated slightly from simulated BSA.

Most observed data is contained within the 95% prediction interval of the model predictions. However C_{max} seems to be somewhat underpredicted in the youngest children with the highest observed C_{max} being about 30% higher than the upper limit of the 95% prediction interval.

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