External Evaluation of a Population Pharmacokinetic Model for Dosing Busulfan in Children – Body Surface Area better than Body Weight

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Background and Objectives

High - dose Busulfan

Busulfan, a DNA-alkylating agent, is used in high-dose conditioning regimens prior to bone marrow transplantation in children and adults for haematological malignancies.

Busulfan has a narrow therapeutic range with side effects such as veno-occlusive disease (VOD) when toxicity increases due to high busulfan exposure or low engraftment rates due to less efficacy by low busulfan exposure.

Therefore, given the high interindividual variability, busulfan requires precise dosing recommendations for children. According to the labelling of i.v. busulfan in children, dosing is based on five weight-based dosing groups (Fig. 2; Nguyen L, et al. Bone Marrow Transplant 2004; 33:979-87). Taking into consideration that there is no linearity in the relationship between body weight and BSA it remains unclear whether weight-based dosing or an individual BSA dosing is the best method for dosing busulfan in children.

Objectives

A previously developed population pharmacokinetic model to evaluate the best method for dosing busulfan in children was tested by external evaluation using pharmacokinetic data from children receiving a different schedule of administration.

Patients and Methods

Development Dataset

- 94 children received busulfan prior to bone marrow transplantation
- median age 9.51 (range 0.9 – 18.8 years)
- 48 children received oral busulfan every 6 h
  - 41 received between 13 and 20 mg/kg
  - 7 received a dose of 600 mg/m^2
- 46 children received IV busulfan as an infusion
  - first dose was given as a double dose (1.4 – 2.0 mg/kg) over 4 h
  - followed 12 h later by 15 single doses (0.7 – 1.0 mg/kg) every 6 h

Evaluation Dataset

- 24 children received IV busulfan once daily as a 3 h infusion
  - first dose in patients > 1 year: 120 mg/m^2
  - first dose in patients < 1 year: 80 mg/m^2
  - followed by doses evaluated through TDM
- all plasma samples were analysed either by HPLC using postcolumn photolysis or by LC-MS with a LOQ of 5 µg/L
- reduced sampling method
- plasma concentration-time data were analysed using NONMEM VI

Plasma Sample Collection

- plasma samples drawn during routine drug monitoring in children receiving busulfan
- plasma samples were taken 4 – 5 times during the whole dose regimen prior to next dose

Pharmacokinetic Analysis

- one-compartment model with 1st-order absorption
- FOCE Interaction
- residual variability was modelled using a proportional error model
- exponential model for IIV and IOV
- covariates
  - BSA as a covariate for clearance (Cl/F) and volume of distribution (V/F)

Results

A one-compartment model with BSA as a covariate for clearance (Cl/F) and volume of distribution (V/F) described the busulfan kinetics of the development dataset sufficiently (table 1). Estimation of the population parameters of the evaluation dataset on the basis of the development model resulted in very similar population values compared to the development dataset (table 2). Furthermore, the precision, robustness and predictability of the model can be seen in figure 2 and 3 of the development and the evaluation dataset.

	Pop. Mean	IIV %	IOV %
Cl [L h^{-1} m^{-2}]	4.2 (5%)	27 (19%)	10 (21%)
V [L m^{-2}]	19.0 (7%)	35 (35%)	22 (18%)
ka [1/h]	0.963 (22%)	91 (31%)	.
F [%]	91 (7%)	.	.
prop. error [%]	27 (6%)	.	.

IIV = interindividual variability; IOV = interoccasion variability

Table 1: Development dataset - results of the population pharmacokinetic analysis; standard errors in brackets

	Pop. Mean	IIV %	IOV %
Cl [L h^{-1} m^{-2}]	4.9 (6%)	15 (117%)	29 (15%)
V [L m^{-2}]	15.5 (9%)	31 (43%)	0.0 (601%)
ka [h^{-1}]	0.963 FIX	91 FIX	.
F [%]	91 FIX	.	.
prop. error [%]	17 (14%)	.	.

IIV = interindividual variability; IOV = interoccasion variability

Table 2: Evaluation dataset - results of the population pharmacokinetic analysis; standard errors in brackets

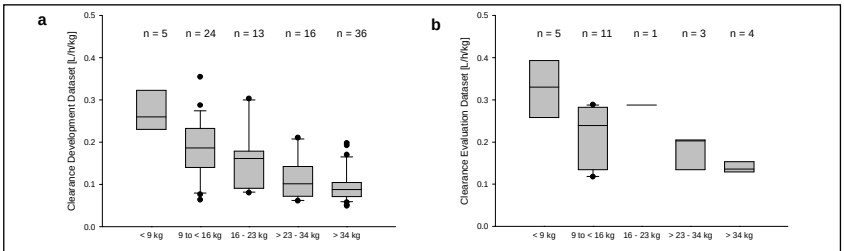

Figure 1: Clearance in different weight strata; plots the median, 10th, 25th, 75th, and 90th percentiles as vertical boxes with error bars; (**a**) development dataset; (**b**) evaluation dataset

We cannot confirm the lower clearance in the group < 9 kg as expected from the dosing recommendation in the labelling of Busulfex® (EMA). In the population of the development dataset as well as in the evaluation dataset these children have a higher clearance.

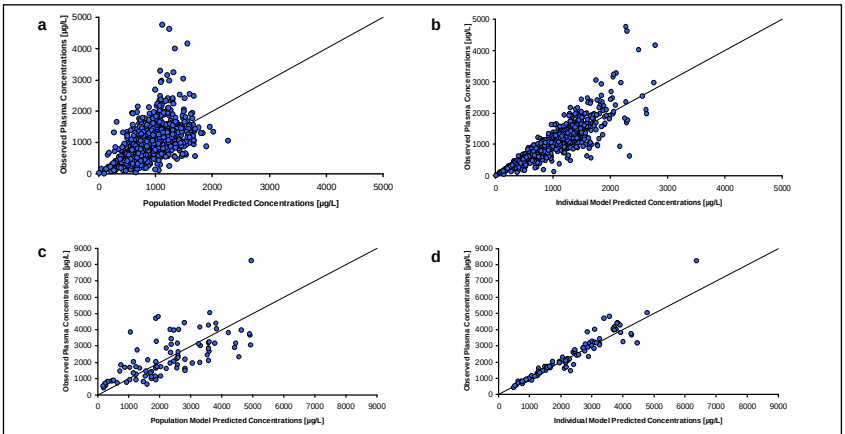

Figure 2: Goodness-of-fit plots: (**a, b**) development dataset; (**c, d**) evaluation dataset

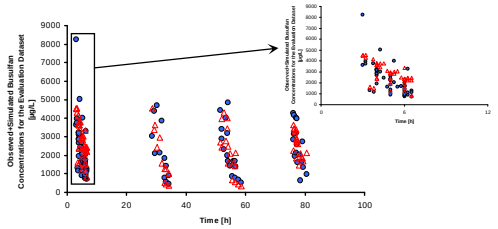

Figure 3: Simulated busulfan concentrations for the evaluation dataset on the bases of the development model and the observed busulfan concentrations of the evaluation dataset versus time; blue dots = observed busulfan concentrations; red triangles = simulated busulfan concentrations

Conclusion

• By external model evaluation and simulation we were able to confirm the findings and show precision, robustness and predictability of the model with data from different dosing and different schedule of administration.
• With this evaluation we could further confirm our previous findings that in the paediatric population, BSA, not body weight, is the best predictor for Cl/F and should be considered for dose adjustment.