Busulfan Dosing in Children: Body Weight *versus* Body Surface Area or Allometric Body Weight Dosing

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Background and Objectives

- Busulfan is frequently used in high-dose conditioning regimens prior to bone marrow transplantation in children
- Aim of this analysis was to evaluate whether the current licensed EMA dosing recommendation of IV busulfan (Busilvex®) according to body weight (BW) is appropriate for dosing busulfan in children and if a more precise dosing recommendation can be suggested
- Due to the narrow therapeutic index of busulfan with an AUC of 900 – 1500 µM*min it was of particular interest to compare the area under the curve (AUC) of a BW based dosing regimen[1] as recommended in the labelling of Busilvex® with other dosing regimens such as a body surface area (BSA) based dosing regimen

Patients

Model Development Dataset

- 94 children received busulfan prior to bone marrow transplantation
- Median age 9.2 years (range 0.4 – 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

Model Evaluation Dataset

- 24 children, median age 2.6 years (range 0.1 – 18.9 years), 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

Plasma Sample Collection and Analysis

- Plasma samples were drawn during routine drug monitoring in children receiving busulfan
- 4 – 5 samples per dosing regimen prior to next dose
- All plasma samples were analysed either by HPLC using postcolumn photolysis or by LC-MS with a LOQ of 5 µg/L

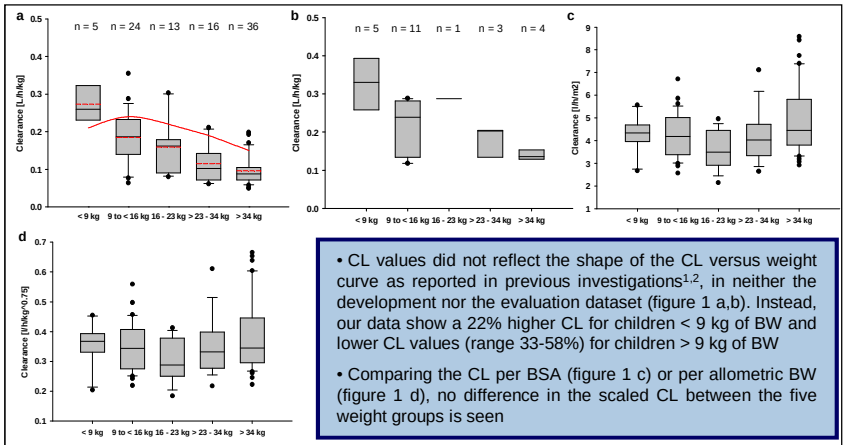
Population Pharmacokinetic Analysis

- Plasma concentration-time data were analysed using NONMEM VI
- 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 or BW^0.75 as a covariate on clearance (CL) and BW as a covariate on volume of distribution (V)

	Base model	BSA model	Allometric BW model
Fixed effects			
CL [L h^{-1}]	3.1 (9%)	4.2 m^{-2} (4%)	4.1 kg$^{-0.75}$ (3%)*
V [L]	15.3 (11%)	18.4 kg^{-1} (5%)*	18.3 kg^{-1} (5%)*
k_a [h^{-1}]	0.963 (23%)	1.03 (18%)	0.983 (18%)
F [%]	61 (11%)	93 (4%)	99 (11%)
BW_factor on V [%]		3.42 (6%)	2.52 (5%)
Random effects			
Interindividual variability			
CL [%]	47 (10%)	23 (10%)	21 (10%)
V [%]	56 (12%)	29 (19%)	24 (24%)
k_a [%]	100 (14%)	95 (15%)	104 (14%)
F [%]**	29 (21%) [0.72]	19 (24%) [2.55]	25 (49%) [10.4]
Intraindividual variability			
CL [%]	10 (27%)	11 (21%)	11 (21%)
V [%]	20 (26%)	21 (22%)	22 (21%)
Residual error			
proportional [%]	27 (7%)	27 (6%)	27 (6%)
Objective function	10842	10669	10664

Table 1: Population model comparison [Abbreviations: *BW* body weight, *BSA* body surface area, *CL* clearance, *V* volume of distribution, k_a absorption rate constant, *F* bioavailability, standard errors in brackets, * estimated for a 27.2 kg subject, ** CV% based on simulations (sd(Fi)/mean(Fi)) and in squared parenthesis shows the variance for the logit-transform of F]

Results



- CL values did not reflect the shape of the CL versus weight curve as reported in previous investigations[1,2], in neither the development nor the evaluation dataset (figure 1 a,b). Instead, our data show a 22% higher CL for children < 9 kg of BW and lower CL values (range 33-58%) for children > 9 kg of BW
- Comparing the CL per BSA (figure 1 c) or per allometric BW (figure 1 d), no difference in the scaled CL between the five weight groups is seen

Figure 1: Clearance in different weight strata; (**a**) clearance for the development dataset per BW; dashed and solid red lines: mean clearance values from a previous investigation[2]; (**b**) clearance for the evaluation dataset per BW; (**c**) clearance per BSA; (**d**) clearance per allometric body weight; plots the median, 10th, 25th, 75th, and 90th percentiles as vertical boxes with error bars

By external model evaluation and simulation using prediction corrected Visual Predictive Checks[3] we were able to confirm the models (figure 2).

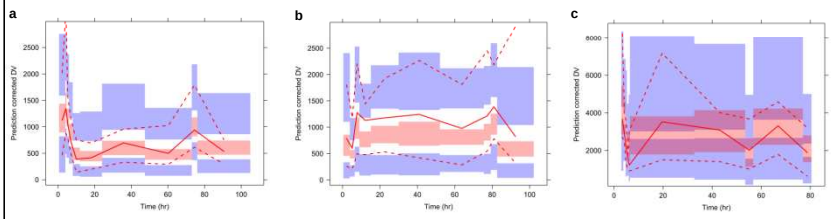


Figure 2: prediction corrected Visual Predictive Checks (pcVPC); (**a**) development models with IV busulfan data; (**b**) development models with oral busulfan data; (**c**) evaluation dataset; pcVPCs show the median (solid red line), 5th and 95th percentiles (dashed red lines) for the observed data with 95% confidence intervals for the median (red field), 5% and 95% percentiles (blue fields) based on simulations

Based on the final models, two dosing schemes for dosing IV busulfan according to BSA and allometric BW were simulated, showing that about 30% more patients were estimated to be within the proposed therapeutic AUC range of 900-1500 µM*min. Further, using these dosing regimens a decrease in the AUC variability compared to the labelled EMA dosing recommendation was achieved (figure 4).

BSA dosing regimen

Dose (mg) = 4.72* mg h L^{-1} × 4.16 L h^{-1} m^{-2} × BSA m^2 = 19.6 mg m^{-2} × BSA m^2

Allometric BW dosing regimen

Dose (mg) = 4.72* mg h L^{-1} × 4.11 L h^{-1} kg$^{-0.75}$ × (BW/27.2) kg$^{0.75}$ = 19.4 mg kg$^{-0.75}$ × (BW/27.2) kg$^{0.75}$

*AUC_{target} = 1150 µmol min L^{-1} = 4.72 mg h L^{-1}

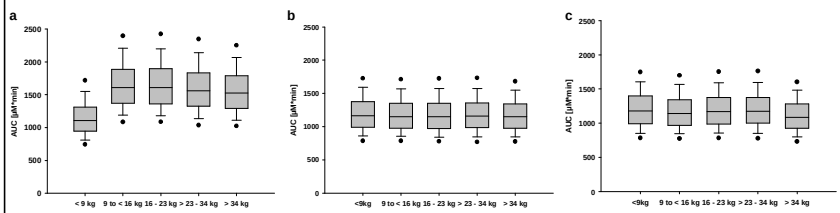


Figure 4: AUC simulations for the different dosing regimens with an AUC_{target} of 1150 µM*min; (a) EMA dosing regimen; (b) allometric body weight dosing regimen; (c) BSA dosing regimen; plots the 10th, 25th, 50th, 75th and 90th percentiles as vertical boxes with error bars [Abbreviations: *AUC* area under the curve, *BW^0.75* allometric body weight, *BSA* body surface area, *EMA* European Medicine Agency]

References

1) Nguyen L et al. I.V. Busulfan in pediatrics: a novel dosing to improve safety/efficacy for hematopoietic progenitor cell transplantation recipients. *Bone Marrow Transplant. 2004;33:979-987*
2) Vassal G et al. Prospective validation of a novel IV busulfan fixed dosing for paediatric patients to improve therapeutic AUC targeting without drug monitoring. *Cancer Chemother Pharmacol. 2008;61:113-123*
3) Bergstrand M et al. Prediction-Corrected Visual Predictive Checks for Diagnosing Nonlinear Mixed-Effects Model. *AAPS J. 2011*

Conclusion

- The findings of our analysis provide an alternate dose regimen to the EMA dosing recommendation of Busilvex® in children.
- Dose regimens based on BSA and allometric BW provide AUCs closer to the therapeutic target for *a priori* and TDM dose adjustments based on our simulations.
- An update to Busilvex® labelling may be warranted