

Population Pharmacokinetics of Busulfan in Pediatric Patients Undergoing Hematopoietic Stem Cell Transplantation

Engi Algharably^{1*}, Jonathan P. Gross^{2*}, Lina Alasfar², Reinhold Kreutz¹, Johannes H. Schulte², Ahmed A. Abulfathi³

¹Institute of Clinical Pharmacology and Toxicology, Charité – Universitätsmedizin Berlin, Germany

²Department of Pediatric Oncology and Hematology, Charité – Universitätsmedizin Berlin, Germany

³CDDS, Certara USA, Radnor, PA, USA.

* These authors contributed equally to this work

Introduction and Objectives

- Busulfan is used in conditioning regimens prior to allogeneic hematopoietic stem cell transplantation (HSCT).
- Narrow therapeutic index, wide inter- and intraindividual variability, particularly in pediatric patients.
- Therapeutic drug monitoring (TDM) necessary for effective treatment and low toxicity.
- No consensus on TDM protocols → variability in sampling times or frequencies that vary among centers.

We aimed to characterize busulfan pharmacokinetics (PK) using a population approach as a necessary first step to optimize TDM-guided dosing practice in patients undergoing HSCT.

Objectives:

- develop a population PK model to characterize the PK of busulfan.
- quantify and identify the sources of variability of busulfan PK.

Methods

- 62 pediatric patients undergoing HSCT.
- Charité, Berlin; March 2017 – October 2023.
- IV busulfan infusion, q. 12 h, 3–4 days, initial dose: 3.1–5.2 mg/kg¹
- Subsequent dosing is based on cumulative AUC (cAUC).
- Target cAUC² (mg·h/L): 50–70 for reduced-intensity conditioning, and 80–105 for myeloablative conditioning.
- Pre-infusion, and 0, 0.5, 1, 2, 4, 6, 9h post-infusion.**
- After 1st, 3rd, 5th, 7th dose.**
- Nonlinear mixed-effects, FOCE-ELS, Phoenix NLME v8.4 (Certara Inc.).
- First order elimination, nonlinear Michaelis–Menten kinetics were tested.
- Residual error models, including proportional error, were tested.
- Total body weight, body surface area, fat-free mass, normal fat mass, age, sex, malignancy, serum albumin, interacting drugs (paracetamol, metronidazole, fludarabine, voriconazole).

Results

- N= 1,531, 6.3 samples/individual (range: 5.9–49).
- BLQ = 9 samples (4 patients).

Patients' Characteristics

Characteristic	Value
Age (yr) (median, range)	4.3 (0.25–20.25)
Weight (Kg) (median, range)	17.1(4.8–78)
Sex (N, %)	38 (61%)
Malignancy (N, %)	18 (29%)
Baseline albumin (mg/L)	38.7 (30.5–47.2)
No. of busulfan doses (median, range)	8 (2–9)
No. of TDM (median, range)	4 (1–8)

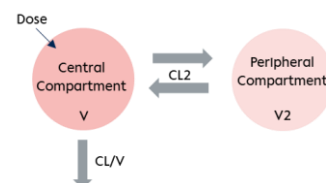
Pop PK Model Parameters

Parameter (units)	Estimate (RSE%)	BSV [Shrinkage %]
CL (L/h)	3.52 (4.97)	30 [6.3]
V (L)	9.98 (4.15)	32.8 [10.8]
CL2 (L/h)	0.38 (12.57)	56.5 [30]
V2 (L)	6.96 (35.3)	38.7[80]
BOV (%)	2.6	--
PMA ₅₀	0.93 (12)	--
Hill coefficient	2.64 (31.7)	--
Proportional error	22.4 (7.9)	--
Eps shrinkage (%)	9.2	--

BSV, between subject variability, BOV, between occasion variability

Pop PK Model Structure

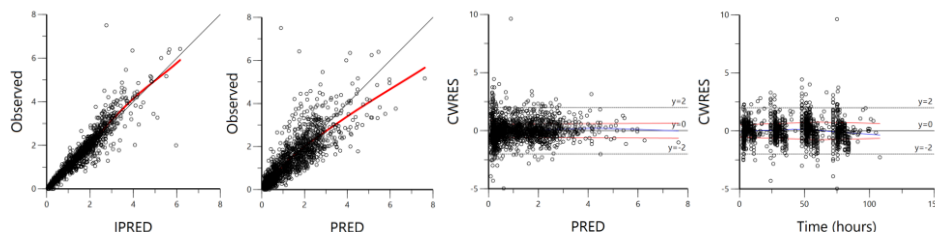
- 2-compartment model with zero-order infusion and first order elimination.
- Between subject variability (BSV) on CL, V, CL2, V2 was included.
- Between occasion variability (BOV) (Day 1–4) on CL improved the model fit.



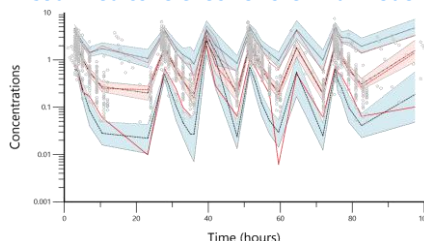
Pop PK Summary Results

- Significant covariates included a body size descriptor as total body weight (TBW) on CL, CL2, V, V2 with allometric scaling as a power function with empirical, fixed values of 0.75 (CL, CL2) and 1 (V, V2).
- A maturation component was incorporated into the CL using a sigmoid E_{max} model based on postmenstrual age (PMA) to account for metabolic ontogeny.
- Sex, malignancy, baseline serum albumin and interacting co-medications (paracetamol, metronidazole, fludarabine, voriconazole) did not improve the model performance.

Goodness of Fit Plots



Visual Predictive Check of the Final Model



The Final Model's Equations for CL Prediction

$$CL(L/h) = CL_{\text{base}}(L/h) \times \left(\frac{TBW}{17.1}\right)^{0.75} \times \frac{PMA^{2.64}}{PMA^{2.64} + 0.82}$$

$$\text{Maturation Factor} = \frac{PMA^H}{PMA^H + PMA_{50}^H}$$

PMA₅₀: PMA at which 50% of adult function is reached
H: Hill coefficient

Conclusions

A two-compartment PK model with linear elimination adequately characterizes the PK of busulfan in pediatric patients undergoing conditioning therapy. This model will be used to enhance TDM-guided dosing, aiming to achieve target cumulative AUC levels throughout the treatment period and reduce the time required to reach these target exposures.

References

- Bartelink et al. Clin Pharmacokinet 2012; 51 (5): 331–345
- Bartelink et al. Lancet Haematol 2016; 3: e526–36