

Personalizing Busulfan Dosing in Hematopoietic Cell Transplantation

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Introduction

- Busulfan is an alkylating agent, commonly used in hematopoietic stem cell transplantation (HCT) conditioning regimens.
- Busulfan has a narrow therapeutic window, high interindividual variability (IIV) and a well-established correlation between drug exposure and drug efficacy and toxicity.
- Busulfan is administered intravenously (Q6H/Q24H) or orally (Q6H).
- Model-informed precision dosing (MIPD) is commonly used to individualize dosing in clinical practice. However, current PopPK models have key limitations:
 - Most were developed based on specific populations (adults or children), limiting its use across age groups.
 - PopPK models for oral busulfan are scarce and often based on small datasets with sparse sampling.
 - Infusion lag time due to tubing dead space is often ignored, potentially affecting AUC estimation.

Objectives

- To develop a unified population PK model for oral and IV dosing in HCT patients of all ages.
- To explore the effect of infusion lag time on model performance.

Methods

Study design: Retrospective study among patients of any age who received IV or oral BU as a part of HCT and underwent intensive PK blood sampling to personalize BU doses.

Table 1. Patient characteristics and Bu dosing and sampling data.

Number of patients		527
Number of observations		5329
Children, number (%)		253 (48)
Adults, number (%)		274 (52)
Age, years, Median (IQR) [Range]		22 (5-53.5) [0.16-75]
Male, number (%)		302 (57.3)
Dosing regimen and Frequency	PO_Q6H	218 (41.4)
	IV_Q6H	235 (44.6%)
	IV_Q24H	74 (14%)
Samples per dosing interval		10

- NONMEM software (version 7.4, Icon Development Solutions, Hanover, MD, USA)

Results

- Oral (Q6H) and IV (Q6H, Q24H) data were combined to develop a PopPK model for busulfan.
- A two-compartment disposition model with first-order elimination and first-order absorption best described the data.
- Weight was included on all PK parameters with fixed exponents.
- A time-dependent residual error model was assessed to account for higher uncertainties in samples taken early (during absorption or infusion).
- Maturation of CL with age was best described using a sigmoid Emax model.
- Estimation of lag time in pediatrics (below 2 years of age) with IIV resulted in the best improvement in model fit.
- None of the covariates examined (albumin, haemoglobin, sex, malignancy status) were retained in the final model after a stepwise covariate model (SCM) building approach.

Final PopPK model

Table 2. Parameter estimates of the final population pharmacokinetic model, including NONMEM estimates with uncertainty.

Parameter	Description	Estimate (RSE)
Structural model		
CL (L/h/70 kg)	Clearance scaled to a total body weight of 70 kg	11.2 (2.8)
V1 (L/70 kg)	Central volume of distribution scaled to a total body weight of 70 kg	49.1 (1.5)
Q (L/h/70 kg)	Inter-compartmental clearance scaled to a total body weight of 70 kg	1.71 (13.3)
V2 (L/70 kg)	Peripheral volume of distribution scaled to a total body weight of 70 kg	211 (14)
Ka (h ⁻¹)	Absorption rate constant	2.23 (7.5)
Lag_abs (h)	Absorption lag time	0.21 (1.8)
Lag_inf (h)	Infusion lag time	0.09 (24.7)
F1	Bioavailability	0.95 (1.9)
FT1_CI	Fraction of 0–6 h clearance >6 h	0.93 (1.2)
Factor	Factor for time-varying residual error	3.6 (7.4)
Random effects		
IIV_CL (%CV)	Inter-individual variability in CL	26.5 (4.8)
COV(CL,V1) (%CV)	Covariance between IIV_CL and IIV_V1	76.7 (0.0)
IIV_V1 (%CV)	Inter-individual variability in V1	22.2 (5.2)
IIV_Q (%CV)	Inter-individual variability in Q	75.2 (10.3)
IIV_Lag_inf (%CV)	Inter-individual variability in infusion lag time	143.7 (20.7)
IOV_CL (%CV)	Inter-occasion variability in CL	9.7 (10.4)
IOV_KA (%CV)	Inter-occasion variability in Ka	126.6 (6.2)
Residual error model		
Prop_RUV (%CV)	Proportional residual error	6.7 (7.5)
Add_RUV (STD), mg/L	Additive residual error	0.00015 (50)

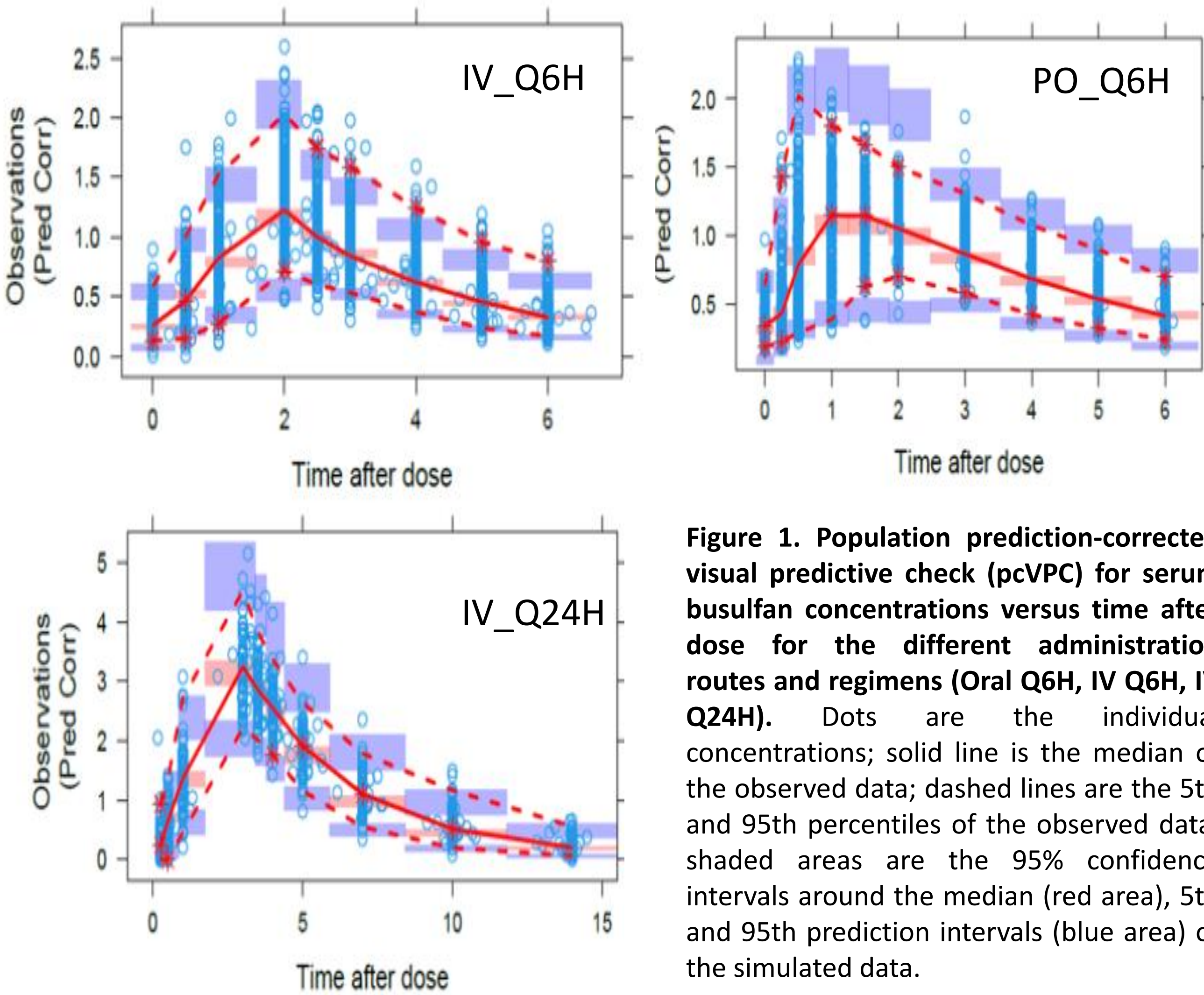


Figure 1. Population prediction-corrected visual predictive check (pcVPC) for serum busulfan concentrations versus time after dose for the different administration routes and regimens (Oral Q6H, IV Q6H, IV Q24H). Dots are the individual concentrations; solid line is the median of the observed data; dashed lines are the 5th and 95th percentiles of the observed data; shaded areas are the 95% confidence intervals around the median (red area), 5th and 95th prediction intervals (blue area) of the simulated data.

Conclusions

Using a unified model to describe the PK of diverse populations (adults and children) and administration routes (IV and oral) is feasible. We are planning to implement this model in daily clinical practice.