

A Physiologically-Based Pharmacokinetic Model for Busulfan

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Introduction

Busulfan (Bu) [figure 1], a DNA-alkylating agent, is widely used for conditioning prior to hematopoietic stem cell transplantation in children and adults. Despite years of clinical research, there are still open questions regarding the optimal dose and schedule of i.v. Bu chemotherapy.

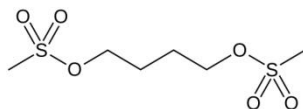


Figure 1: Chemical structure of busulfan

Physiologically-based pharmacokinetic modelling (PBPK) is an approach to better describe and understand the distribution and elimination of drugs in the body and to predict the pharmacokinetics based on drug properties and patient characteristics. In the presented work, a PBPK-model for adults was developed with the aim to predict plasma concentration-time curves, e.g. in children and other special patient groups.

Data and Methods

PK-Sim® (Bayer Technologies, Leverkusen, Germany) was used to develop a PBPK-model. Several physicochemical parameters (e.g. molecular weight, lipophilicity) of Bu were implemented into the PBPK-model.

In terms of its distribution, < 10% of Bu is reversibly bound to plasma proteins [1,2]. Hence, we used a plasma fraction unbound value of 0.93. To consider both, alkylating properties and irreversible binding in plasma [1,2], which are consistent with its reactive electrophilic properties, we increased the partition coefficients from plasma to the intracellular subcompartment using a global factor of 1.1 in all tissue subcompartments.

An increased permeability from plasma to red blood cells (RBC) reflects the binding to RBC described in the literature [1].

Metabolism was implemented in the liver and the small intestine using the activity of glutathione S-transferase (GST) A1, the predominant isoform of GST catalyzing Bu biotransformation [3,4,5]. A value for K_m was found in the literature [4]. As GST A1 is predominantly found in cytosolic protein, in vitro-in vivo extrapolation of V_{max} proved to be difficult. Hence, we estimated V_{max} which resulted in two model parameterizations: a first parameterization with individual V_{max} values for each patient and a resulting second model parameterization with the mean V_{max} value of all patients [table 1].

Table 1: Michaelis-Menten kinetics for busulfan-glutathione conjugation

Organ	Parameter	K_m [μmol/l]	Cyt. protein mass / tissue [mg/g]	V_{max} [pmol/min/mg cyt. protein]	
				$V_{max_{ind}}$	$V_{max_{mean}}$
Liver	GST-A1	3680	80	3400 - 11000	6088
Small intestine	GST-A1	3680	18	3400 - 11000	6088

Bu plasma concentration-time curves of 108 adults with 13 patients receiving Bu four times daily and the remaining receiving a once-daily schedule, were simulated and compared to measured plasma concentrations. Subsequently, appropriateness of the $V_{max_{mean}}$ model was evaluated with an external dataset consisting of 95 adults with five plasma samples drawn after the first once-daily dose [6]. Patients' characteristics are described in table 2.

Table 2: Patients' characteristics

Parameter	Development dataset	Evaluation dataset
Subjects	108 patients (male: 58, female: 50)	95 patients (male: 61, female: 34)
Age [years]	21 – 66 (mean: 51.5)	17 – 66 (mean: 47.1)
Size [cm]	152 – 197 (mean: 171.1)	152 – 193 (mean: 172.9)
Weight [kg]	48 – 127 (mean: 77.3)	42 – 128 (mean: 78.2)

Discussion

Both developed model parameterizations appear to reflect the reality sufficiently with the $V_{max_{ind}}$ parameterization being more precise. The variation for V_{max} value is in close agreement with previous investigations showing a 7- to 8-fold variation in GST-A amount by immunoblot analysis and busulfan-glutathione conjugation [4]. The model can be very helpful to better explain the well known wide variability in the Bu clearance by quantifying the contribution of certain factors such as GST polymorphisms.

Further investigations on distribution processes in different organs and the influence of different comedication are ongoing. Moreover, clearance scaling of the model to investigate the predictive value of the presented model in children is planned.

References

[1] Ehrsson H, Hassan M. J Pharm Pharmacol. 1984 Oct; 36(10):694-6
[2] Hassan M, Oberg G, Ehrsson H et al. Eur J Clin Pharmacol. 1989; 36(5):525-30
[3] Czerwinski M, Gibbs JP, Slattery JT. Drug Metab Dispos. 1996 Sep; 24(9):1015-9.

[4] Bredschneider M, Klein K, Mürdter TE et al. Clin Pharmacol Ther. 2002 Jun; 71(6):479-87
[5] Gibbs JP, Yang JS, Slattery JT. Drug Metab Dispos. 1998 Jan; 26(1):52-5.
[6] Kangarloo SB, Naveed F, Ng ES et al. Biol Blood Marrow Transplant. 2012 Feb; 18(2):295-301. Epub 2011 Jul 27.

Results

Both PBPK model parameterizations of Bu in adults were able to successfully describe the observed Bu concentrations taken from the development dataset [figure 2].

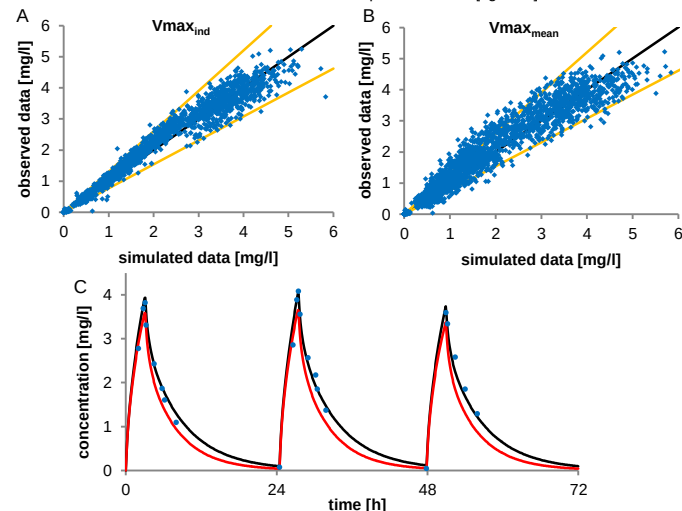


Figure 2: A+B: Goodness-of-fit plot for the development dataset for the first parameterization with individual V_{max} values (A) and resulting second model parameterization with a mean V_{max} value for all patients (B), solid black line = line of identity, solid orange lines = $\pm 30\%$ range
C: Plasma concentration-time curve for patient #12 simulated with the individual V_{max} value (4000 pmol/min/mg cyt. protein, solid black line) and with the mean V_{max} value (6088 pmol/min/mg cyt. protein, solid red line), blue dots = observed concentrations

Figure 3 shows the results for external model evaluation of $V_{max_{mean}}$ parameterization.

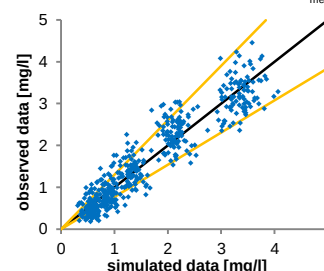


Figure 3: Goodness-of-fit plot for the evaluation dataset for the second model parameterization with a mean V_{max} value for all patients, solid black line = line of identity, solid orange lines = $\pm 30\%$ range

In addition, the pharmacokinetic (PK) parameters AUC, clearance (Cl) and volume of distribution (V) were compared with the results from a non-compartmental analysis (Pharsight WinNonlin® version 5.01) from Kangarloo et al. [6]. The mean absolute prediction error (MAPE) was calculated according to equation 1:

$$MAPE = \frac{\sum(APE)}{N} \quad (Eq. 1)$$

where N is the total number of patients in the evaluation dataset and APE is the absolute prediction error, expressed as a percentage, based on individual PK parameters for each patient according to $100 \times (PK \text{ parameter}_{PK-Sim} - PK \text{ parameter}_{WinNonlin}) / PK \text{ parameter}_{WinNonlin}$. Results are summarised in table 3.

Table 3: Results for pharmacokinetic parameters AUC, Cl and V for the evaluation dataset ($V_{max_{mean}}$ model)

Parameter	Median simulated PK parameter	MAPE [%]
AUC _{inf} [mg*min/ml]	1.17 (range: 0.81 – 1.54)	28.29 (APE range: 0.01 – 111.21)
Clearance [l/h/kg]	0.15 (range: 0.09 – 0.24)	20.72 (APE range: 1.54 – 52.13)
Volume of distribution [l/kg]	0.65 (range: 0.51 – 0.80)	10.64 (APE range: 0.08 – 43.11)