

A Nonparametric, Multiple-Model Approach to Optimize Initial Dosing and Attainment of a Target Exposure Interval: Application to Busulfan in Pediatrics



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Introduction

The traditional approach for model-based initial dosing is based on the use of a single vector of typical population parameters for targeting a specific exposure. This approach is theoretically ill-suited for targeting a range of exposure. The objective of this work was to develop a general approach for optimal targeting of a drug exposure interval. An application to a *priori* model-based dosing of busulfan (Bu) in children is presented as a case study.

Methods

1. Calculation of individual Bu PK parameter values

- ✓ Data from 163 bone marrow transplanted children treated by IV Bu in Lyon, age= 6.1 ± 5.0 years, IBW= 20.9 ± 13.9 kg
- ✓ Nonparametric population model from Neely et al. [1]: 1-compartment model, age- and ideal body weight-related elimination rate constant (K_e) and volume of distribution (V_d), 29 support-points
- ✓ Bayesian posterior estimates

2. Optimization of a *priori* multiple-model (MM) dosing regimen for each patient

- ✓ Prior distribution of busulfan K_e and V_d based on patient's age and IBW
- ✓ 151 doses of Bu ranging from 0.5 to 2 mg/kg as candidate doses
- ✓ Simulated regimen: 2h-infusion, every 6 hours during 4 days
- ✓ 29 support points $\Rightarrow$ 29 PK simulated profiles for each dose $\Rightarrow$ distribution of 29 AUC values with their probabilities
- ✓ Calculation of the *a priori* probability that the AUC is within Bu target interval for each dose
- ✓ Two targeting modes (TM): maximizing AUC within 900 – 1500 $\mu\text{M}\cdot\text{min}^{-1}$ (TM1); or minimizing AUC $\geq 1500 \mu\text{M}\cdot\text{min}^{-1}$ (TM2)
- ✓ Selection of the dose maximizing the probability of mean AUC within the target range after 1, 2, and 16 doses

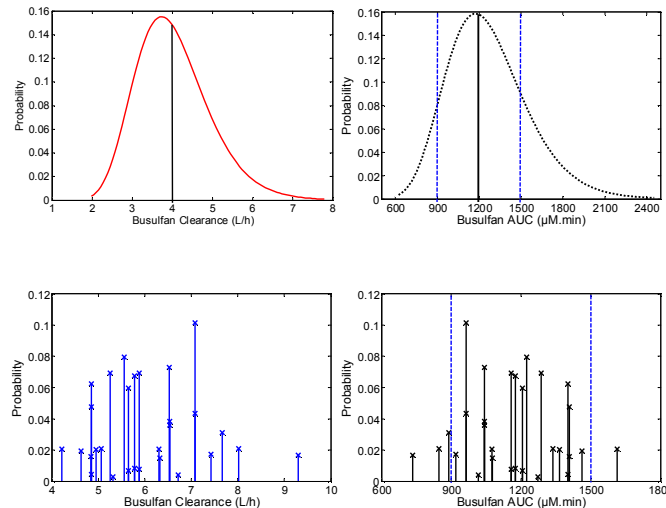


Figure 1. Traditional versus multiple-model approach for a *priori* dosing

Traditional approach (upper panel): prior distribution is continuous but only a point estimate is used to target a single AUC target values (mid AUC range)
MM approach (lower panel): the entire discrete distribution is considered to maximize the probability of achieving the target interval

3. Simulation of selected and alternative model-based regimens

- ✓ Simulation of MM optimal regimens in the 163 children based on their individual "true" PK parameters
- ✓ Simulations of 3 other traditional model-based regimens from EMA [2], Paci et al. [3] and McCune et al. [4], targeting the mid AUC_{ss} range value (1200 $\mu\text{M}\cdot\text{min}$)
- ✓ Individual AUC values after 1, 2 and 16 doses, and comparison of target interval attainment rates

Results

Initial Bu dose based on the MM approach for optimal target attainment			
Dose (mg/kg)	AUC1	AUC2	AUC16
	Targeting mode 1: maximize $900 \leq \text{AUC} \leq 1500 \mu\text{M}\cdot\text{min}$		
Mean $\pm$ sd	1.36 ± 0.06	1.27 ± 0.06	1.16 ± 0.08
Range	1.23 – 1.81	1.11 – 1.63	0.99 – 1.45
	Targeting mode 2: minimize AUC $> 1500 \mu\text{M}\cdot\text{min}$		
	AUC1	AUC2	AUC16
Mean $\pm$ sd	1.34 ± 0.06	1.21 ± 0.05	1.08 ± 0.06
Range	1.24 – 1.82	1.07 – 1.58	0.91 – 1.33

← On average, MM dose was higher than dose based on the others methods, 29.2% higher for AUC1, 22.9% higher for AUC2, and 8.3% higher for AUC16.

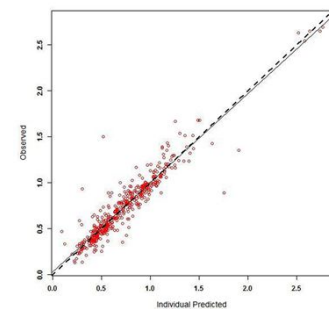


Figure 2. Observed busulfan concentrations versus individual predictions from the Neely model [1] in the 163 children

Dosing method	Percentage of Target Interval Attainment (Busulfan Target AUC: 900 - 1500 $\mu\text{M}\cdot\text{min}$)								
	AUC1			AUC2			AUC16		
	% Within	% Below (% dev.)	% Above (% dev.)	% Inside (% dev.)	% Below (% dev.)	% Above (% dev.)	% Inside (% dev.)	% Below (% dev.)	% Above (% dev.)
MM Targeting Mode 1	82.2*	11.7 (-15.9%)	6.1 (+1.8%)	79.1*	11.7 (-13.5%)	9.2 (+4.2%)	80.4	10.4 (-10.9%)	9.2 (+10.1%)
MM Targeting Mode 2	85.3	14.7 (-8.2%)	0	84.0	16.0 (-14.2%)	0	71.2	28.8 (-9.2%)	0
EMA [2]	31.9	68.1 (-17.6%)	0	54.0	44.8 (-15.5%)	1.2 (+0.2%)	72.4	25.2 (-13.9%)	0.6 (+8.0%)
Paci [3]	26.4	73.6 (-18.0%)	0	46.6	52.8 (-14.6%)	0.6 (1.1%)	69.9	28.2 (-14.4%)	1.8 (+6.1%)
McCune [4]	41.7	58.3 (-15.7%)	0	65.0	35.0 (-14.5%)	0	76.7	19.0 (-3.7%)	4.3 (+4.6%)

* p < 0.005 compared with the best of the three other methods

Conclusions

A multiple-model approach has been designed to optimize the targeting of an exposure interval. When applied to busulfan in children, it outperformed the traditional model-based dosing approach, with earlier and better achievement of busulfan target AUC. It can also address specific dosing issue such as minimizing overexposure. The approach can be applied for optimal dosing of many drugs, when the target objective is an interval.

References: [1] Neely M, et al. *Ther Drug Monit.* 2016;38:332; [2] Nguyen L, et al. *Bone Marrow Transplant.* 2004;33:979; [3] Paci A, et al. *Ther. Drug Monit.* 2012;34:198; [4] McCune JS, et al. *Clin. Cancer Res.* 2014;20:754