Busulfan Dose Recommendation in Inherited Metabolic Disorders: Population Pharmacokinetic Analysis

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Introduction

- Busulfan is a commonly used alkylating agent in conditioning regimen of hematopoietic cell transplant (HCT).
- Busulfan exposure is highly correlated with event-free-survival (optimal area-under-the-curve [AUC]: 78-101 mg·h/L)[1].
- Underlying disease can affect busulfan pharmacokinetics (PK)[2].
- We analyzed population PK (popPK) of busulfan in inherited metabolic disorder (IMD) and developed a dosing regimen to target area-under-the-curve (AUC) of 78 - 101 mg·h/L.

Methods

Design: PopPK analysis and simulation
Patients: 78 patients with IMD had HCT in 2014 – 2020 (**Table 1**)
Therapy: Busulfan/fludarabine (daily x4), serotherapy
Busulfan initial dosing:
  Weight: <12.5 kg   – Based on age and weight (Savic's model[3])
  Weight: 12.5 - 66 kg – Based on weight (Bartelink's model[4])
  Weight: <12.5 kg   – 3 mg/kg/dose
Busulfan PK sampling: 7 times after each of the 1st-3rd doses

PopPK model development:
- Nonlinear Mixed Effect Modeling by software NONMEM 7.5.0
- Estimated PK parameters and random variables
- Covariate testing: Age, weight, body surface area, sex, day of busulfan infusion, diagnosis, co-administered conditioning drugs

Simulation
- Compared predicted clearance in our patients (**Figure 1**)
- Compared predicted time-concentration in our patients (**Figure 2**)
- Derived a dosing regimen from the new model
- Compared target AUC probability by dosing regimen (**Figure 3**)

Table 1. Patient characteristics (n = 78)

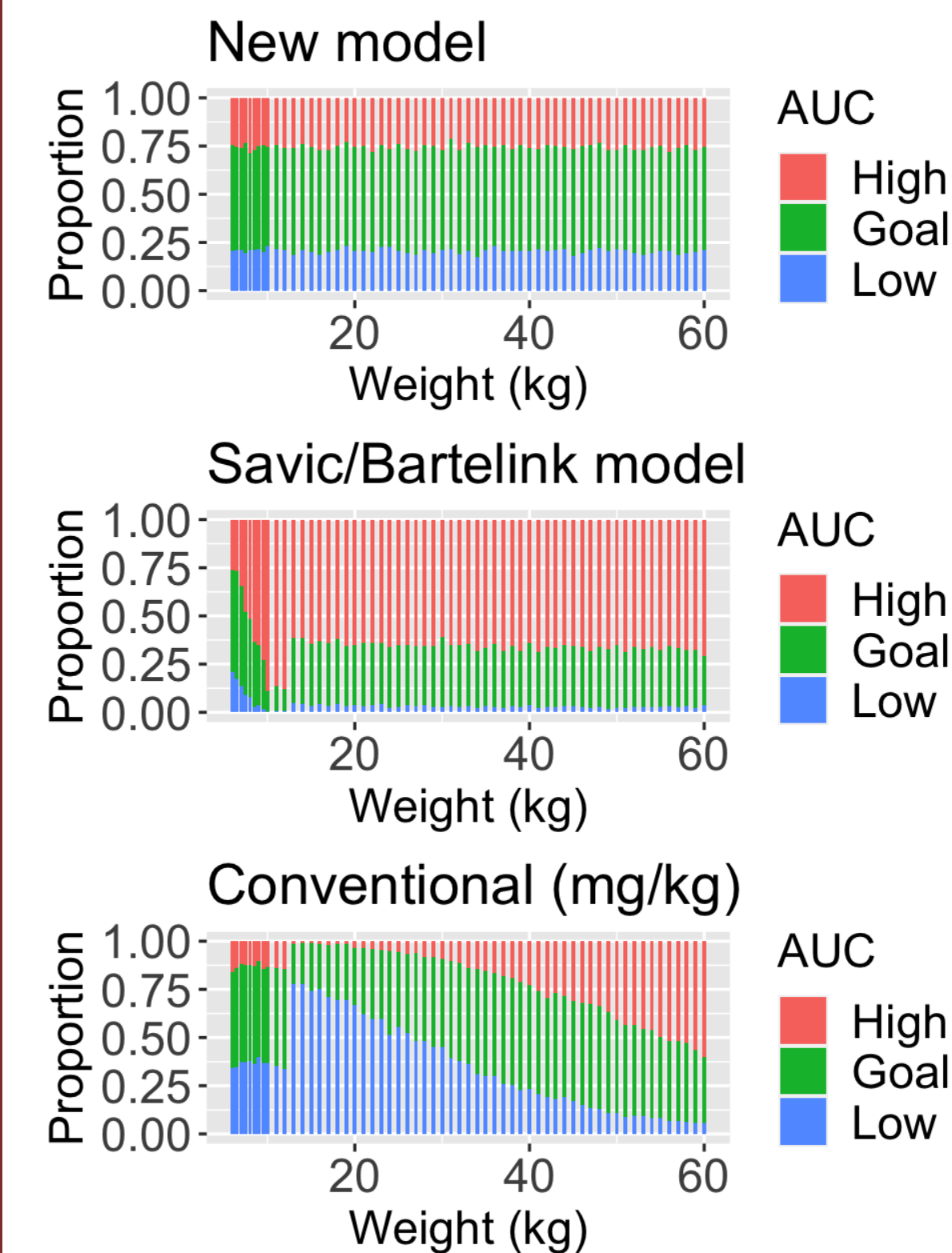| Variables		
Age (years), median, range	2.5	0.1 - 56
Weight (kg) , median, range	16.2	3.1 - 87.3
Diagnosis, N, %		
Adrenoleukodystrophy	24	31%
Hurler/Hunter syndrome	43	55%
Others	11	14%

Figure 3. Target AUC probability
Conventional dose (4.0 mg/kg/dose for weight <12 kg and 3.2 mg/kg/dose for weight ≥12kg)
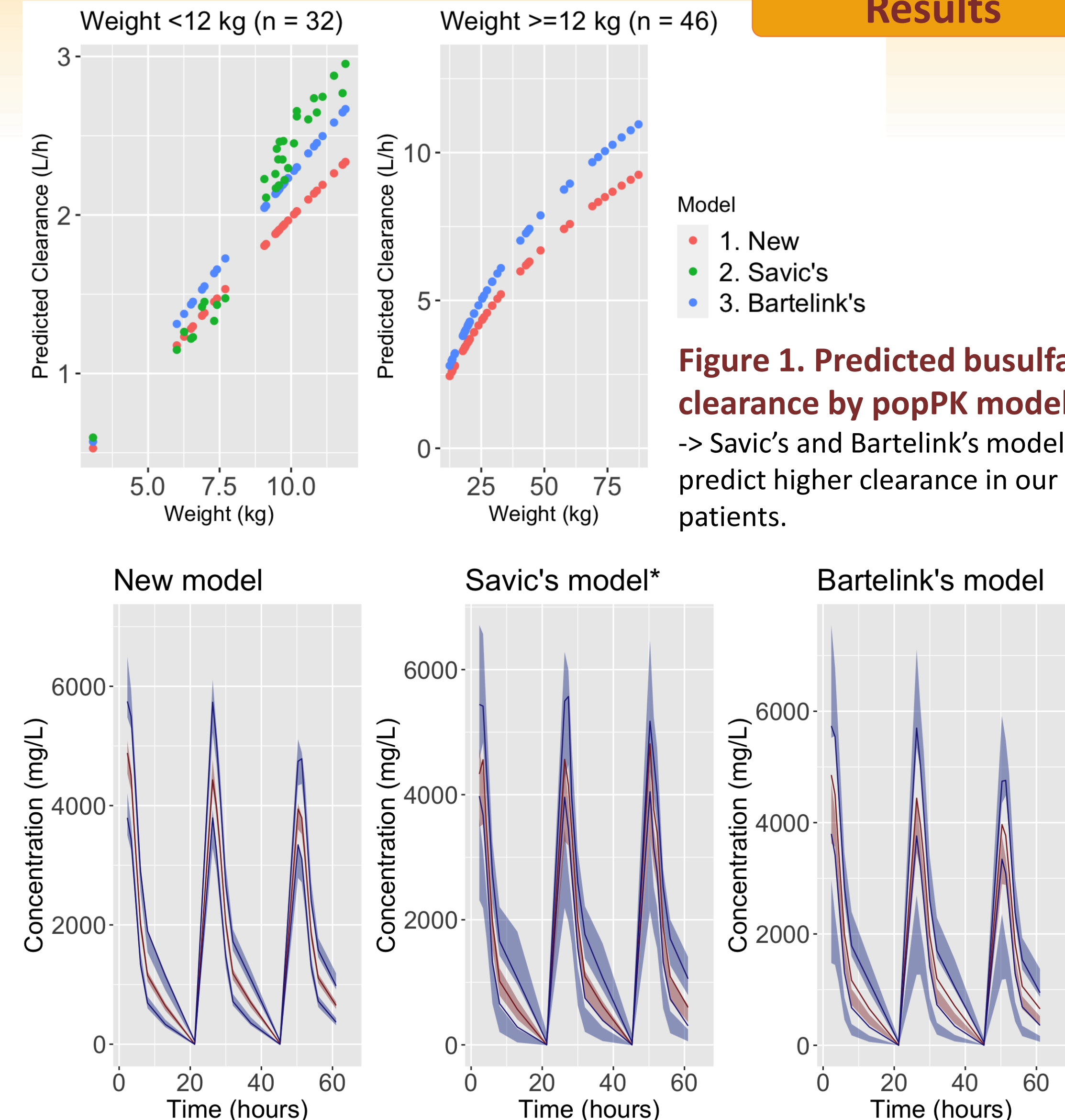-> New model showed the highest goal AUC probability across different weights.

Results

Figure 1. Predicted busulfan clearance by popPK model
-> Savic's and Bartelink's models predict higher clearance in our patients.

Figure 2. Predicted time-concentration by popPK model
-> Savic's and Bartelink's models slightly underpredict concentrations in our patients.

Discussion

1. Busulfan PK in IMD

Previously published popPK models overpredict busulfan clearance in IMD and thus underpredict exposure.

-> These models suggest higher dose, which lead to overexposure. Our new model will improve this overexposure.

2. PK change over 1st – 3rd infusion

Busulfan clearance in IMD showed mild decrease from 1st to 2nd day and minimal decrease from 2nd to 3rd day of infusion.

-> PK study are needed at least after the first 2 doses.

Conclusion

- This dedicated popPK model successfully described **possible unique busulfan PK in IMD** cohort.
- A dosing regimen based on **our model can improve the target AUC attainment** among them.

References: [1] Bartelink, Lancet Hematol. 2016. [2] Bertholle-Bonnet V, Ther Drug Monit. 2007. [3] Savic, BBMT 2013. [4] Bartelink, Ther Drug Monit 2012.