Population pharmacokinetics of dimethylacetamide in children receiving intravenous busulphan

Sebastian P A Rosser[1], Christa E Nath[2], Andrew J McLachlan[3], Peter J Shaw[1,2]

1. Children's Hospital at Westmead Clinical School, University of Sydney, 2. Department of Oncology, The Children's Hospital at Westmead Sydney, 3. Sydney Pharmacy School, University of Sydney

email: sros6571@uni.sydney.edu.au

BACKGROUND

- Administration of busulphan for bone marrow transplant (BMT) conditioning can come at the cost of various neuro- and hepatotoxic effects
- This may be related in part to the solvent *N,N*-dimethylacetamide (DMA) used in intravenous busulphan formulations

AIMS

To build a preliminary pharmacokinetic model for evaluation of DMA in paediatric patients receiving intravenous busulphan for BMT conditioning

METHODS

1. Patient demographics

2. Busulphan conditioning and blood collected

3. DMA concentration determination (LC-MS/MS)

4. Population PK modelling
- **NONMEM (v7.4)**
- **RStudio**

5. Model validation:
- **NP-bootstrap**
- **VPC**

- Blood samples were collected and measured at **0, 1, 2, 4, and 8 h time points**
  - **367 data points** from **18 patients** aged 0.3 – 18 years (median 3.5 years) from the Children's Hospital at Westmead, Sydney
- One- and two-compartment models were tested using NONMEM (v7.4)
- Predictors of **clearance (CL)** and **volume of distribution (V):**
  - **weight (WT), age, body surface area, glomerular filtration rate**
- The best fit model was determined to be that with the **lowest objective function value** (OFV)

RESULTS

A **one-compartment model** was selected

Parameter	Population estimate (%RSE)	IIV (%RSE)	95% CI
Day 1 CL (L/h)	1.03 (10%)	37.5% (21%)	0.83 – 1.12
CL (L/h)	1.43 (6%)	25.9% (16%)	1.27 – 1.60
V (L)	10.3 (4%)	11% (28%)	9.52 – 10.90
Residual variability			
Additive (mg/L)	301		
Proportional	9%		

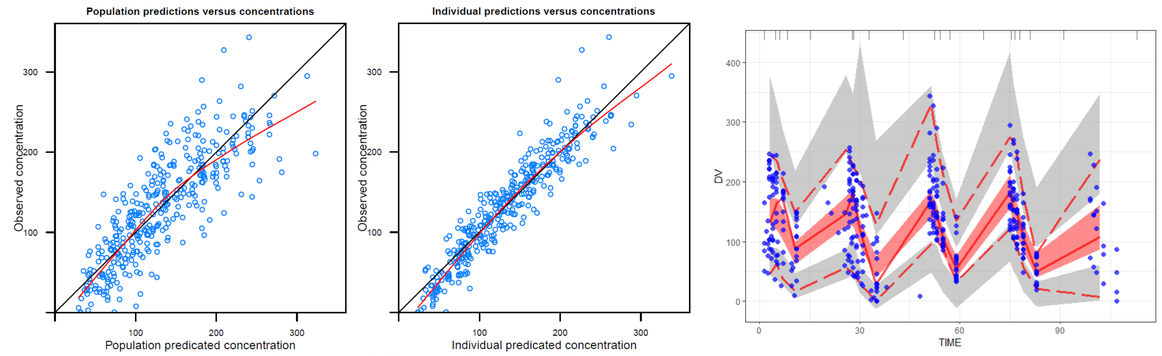
Model equations:

$$CL = TVCL * EXP(\eta(1)) * \left(\frac{WT}{\text{median } WT}\right)$$

$$V = TVV * EXP(\eta(2)) * \left(\frac{WT}{\text{median } WT}\right)$$

OFV before WT covariate: 2782.371

OFV after WT covariate: 2712.511 **(ΔOFV = 69.86)**



Goodness of fit and **VPC** plots show **strong correlation** between model predicted and observed data.

CONCLUSIONS

Correlation with **patient toxicity, and incorporation of metabolite data** is now being investigated