Population pharmacokinetics of dimethylacetamide in children receiving intravenous busulphan

Sebastian P A Rosser[1,2], Christa E Nath[2,3], Andrew J McLachlan[4], Peter J Shaw[1,3]

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

email: sros6571@uni.sydney.edu.au

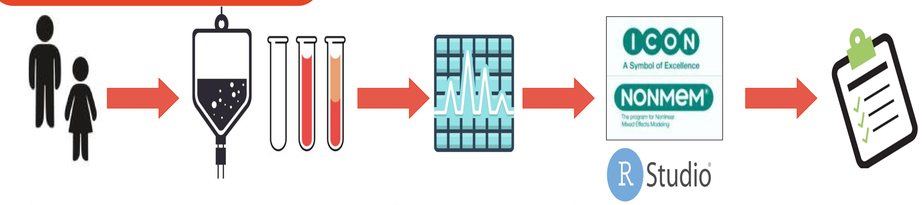
BACKGROUND

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

AIM

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

METHODS



1. **Patient demographics recorded**
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** on each day of busulphan dosing
  - **515 data points** from **27 patients** aged 0.3 – 18 years (median 3 years) from the Children's Hospital at Westmead, Sydney
- Model fitting was assessed through different structural, error, and covariate models and validated through bootstrapping (n = 1000) and simulation based visual predictive checks (n = 1000)
- Predictors of **clearance (CL)** and **volume of distribution (V)** tested**:**
  - **weight (WT), age, body surface area, glomerular filtration rate**
- Area under the curve (AUC) was determined for each individual as **AUC = DMA dose/CL**, and summed across all days to obtain cumulative AUC
- The best fit model was determined to be that with the **lowest objective function value** (OFV)

RESULTS

Final model fit:

Structural model: 1-compartment

Error model: Proportional and additive

Covariate model: Patient weight

Final model equations:

CL = TVCL*EXP(η(1)) * $(\frac{WT}{70\ kg})^{0.75}$

V = TVV*EXP(η(2)) * $(\frac{WT}{70\ kg})$

Y = F * (1 + (ERR(1)) + ERR(2)

TV = typical value (i.e. population value)

η = inter-individual variability (IIV)

0.75 term = allometric scaling factor

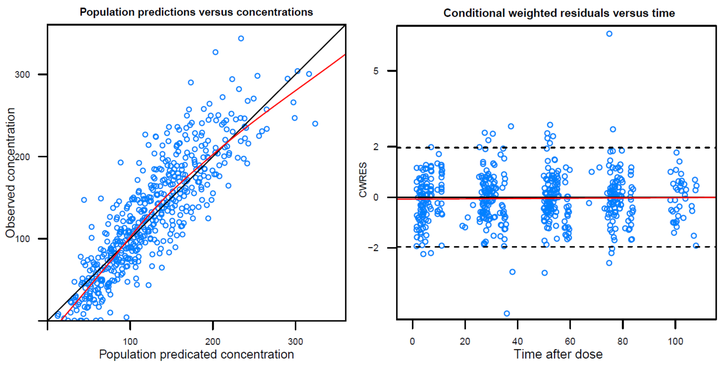
Y = output

F = model prediction

Model estimates

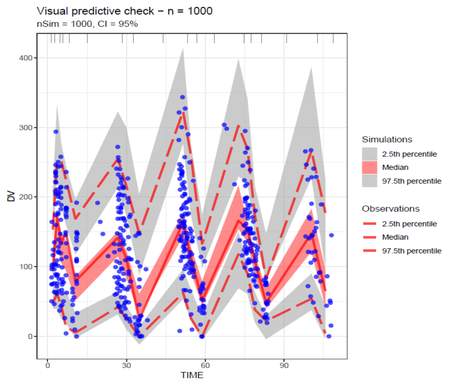
Parameter	Population estimate (%RSE)	IIV (%RSE)	95% CI
Day 1 CL (L/h)	4.11 (10%)	44.9% (20%)	3.47 – 5.02
Day 2 CL (L/h)	7.01 (8%)	38.1% (18%)	5.92 – 8.15
Day 3 CL (L/h)	5.54 (8%)	40.4% (15%)	4.66 – 6.48
Day 4 CL (L/h)	6.54 (6%)	29% (16%)	5.76 – 7.44
Day 5 CL (L/h)	5.84 (14%)	37% (33%)	4.5 – 8.03
V (L)	61.8 (4%)	18.4% (13%)	57.4 – 66.9
Residual variability			
Additive (mg/L)		122	
Proportional		6%	
OFV (ΔOFV from base model)		3588.987 (-713.201)	

Goodness of fit plots



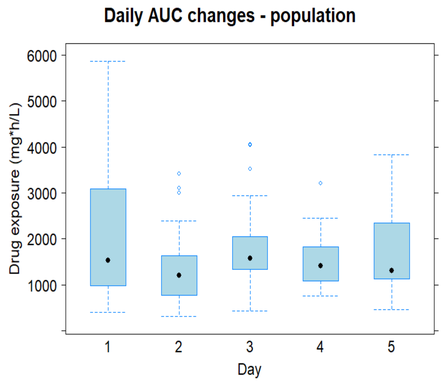
VPC plot

- VPC plot provides a visual assessment for if the model is able to reproduce the variability and trend of the observed data



DMA exposure

- Individual cumulative AUC (median [IQR]): **6902 [4652 – 9233] mg*h/L**
- Day 1 AUC variability is due to the relative uncertainty in the test dose



CONCLUSIONS

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

REFERENCES

[1] Weiss, et al. "A phase I study of dimethylacetamide." Cancer Chemother Rep 16.477 (1962): 1962-485.
[2] Hempel, et al. "Cytotoxicity of dimethylacetamide and pharmacokinetics in children receiving intravenous busulfan." J Clin Oncol 25.13 (2007): 1772-1778.
[3] Trame et al. "Population pharmacokinetics of dimethylacetamide in children during standard and once-daily IV busulfan administration." Cancer Chemother Pharm 72.5 (2013): 1149-1155.