Population Pharmacokinetics of Dimethylacetamide in Children During Once-daily and Standard IV Busulfan Administration

Trame MN[1] · Bartelink IH[2] · Boos J[3] · Boelens JJ[2] · Hempel G[1,3]

[1]Department of Pharmaceutical and Medical Chemistry – Clinical Pharmacy -, University of Muenster, Germany
[2]Department of Haematology, Immunology and Clinical Pharmacy, University Medical Center Utrecht, The Netherlands
[3]Department of Paediatric Haematology and Oncology, University Children's Hospital Muenster, Germany
Contact E-mail: tramemirjam@uni-muenster.de

Background and Objectives

N,N-Dimethylacetamide (DMA) is applied to children during high-dose chemotherapy as a solubilizer with the intravenous (IV) formulation of busulfan (Busilvex®). DMA has shown liver toxicity in rats, but little is known on the pharmacokinetics of DMA in humans.

In a previous investigation (J Clin Oncol 25:1772-1778, 2007), we analysed the pharmacokinetic of DMA in 18 children in a four times daily regimen. The aim of this analysis was to evaluate possible differences in pharmacokinetics of DMA after administration of a once daily dose in comparison with a similar amount, divided over 3-4 administration per day in children.

Patients and Methods

- 43 children received busulfan prior to bone marrow transplantation
- median age 2.7 (range 0.1 – 18.9 years)
- median BSA 0.63 m^2 (range 0.24 – 2 m^2)
- median body weight 15.1 kg (range 4 – 74.2 kg)
- 24 children received IV busulfan once daily as a 3 h infusion
  - first dose in patients > 1 year: 120 mg/m^2
  - first dose in patients < 1 year: 80 mg/m^2
  - followed by doses evaluated through TDM
- 18 children received IV busulfan four times daily as a 2 h infusion
  - first dose was given as a double dose (1.4 – 2.0 mg/kg) over 4 h
  - followed 12 h later by 15 single doses (0.7 - 1.0 mg/kg) every 6 h
- all plasma samples were analysed by LC-MS with a LOQ of 0.25 mg/L
- reduced sampling method
- plasma concentration-time data were analysed using NONMEM VI

Plasma Sample Collection

- plasma samples drawn during routine drug monitoring in children receiving busulfan or during a clinical trial (Anti-Cancer Drugs 16:337-344)
- plasma samples were taken 4 – 5 times during the whole dose regimen prior to next dose
- plasma samples are stored at - 20℃ until analysis

Pharmacokinetic Analysis

- one-compartment model with first order conditional estimation (FOCE)
- residual variability was modelled using a proportional error model with different values for the German and Dutch data set
- exponential model for IIV and IOV
- covariates
  - body weight as a covariate for clearance (Cl) and volume of distribution (V)
  - Cl increasing by 0.0024 ml h^{-2} kg^{-1} during the standard dosing
  - Cl increasing by 0.000258 ml h^{-2} kg^{-1} during the once daily dosing

Results

Using a one-compartment model with clearance (Cl) increasing over time the DMA kinetics were best described. Several covariates were tested on their effects on the pharmacokinetic parameters. By using body weight as a covariate for Cl and volume of distribution (V) the best results were obtained (Table 1). Peak plasma concentrations of DMA up to 3.09 mmol/L (median 0.75 mmol/L) for the standard dosing and up to 8.77 mmol/L (median 3 mmol/L) for the once-daily dosing were observed, respectively.

	Pop. Mean	IIV %	IOV %
$Cl_{initial}$ (ml h^{-1} kg^{-1})	75.5 (15.5%)	45.4% (45.6%)	28.6% (18.2%)
V (ml kg^{-1})	518 (6.9%)	19.3% (86.8%)	.
Cl time factor MS (ml h^{-2} kg^{-1})	0.0024 (30.3%)	.	.
Cl time factor Utrecht (ml h^{-2} kg^{-1})	0.000258 (67.4%)	.	.
prop. error MS	33.4% (20.2%)	.	.
prop. error Utrecht	16.2% (17.2%)	.	.

IIV = interindividual variability; IOV = interoccasion variability

Table 1: Results of the population pharmacokinetic analysis; standard errors in brackets

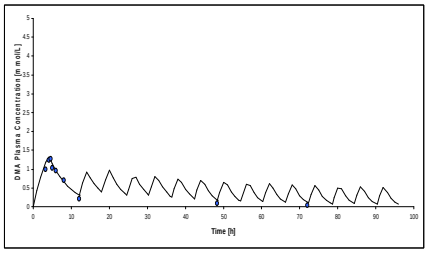

Figure 1: DMA plasma concentrations during standard busulfan dosing regimen for a respresentative patient

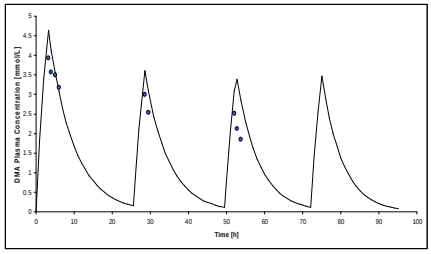

Figure 2: DMA plasma concentrations during once-daily busulfan dosing regimen for a representative patient

The DMA kinetics were best described using a one-compartment model with clearance increasing over time by 58 ml h^{-1} kg^{-1} and 6.1 ml h^{-1} kg^{-1} per day for the standard dosing and once-daily dosing regimen, respectively.

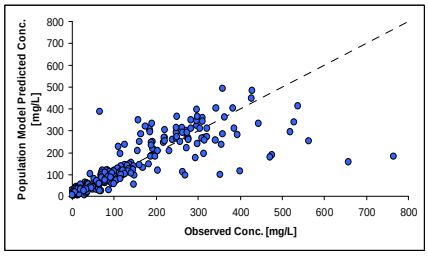

Figure 3: Goodness-of-fit plot for the model predicted concentrations vs observed DMA concentrations for the pediatric patients in the final model

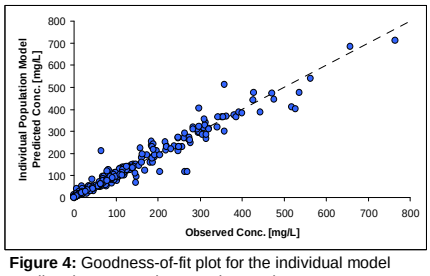

Figure 4: Goodness-of-fit plot for the individual model predicted concentrations vs observed DMA concentrations for the pediatric patients in the final model

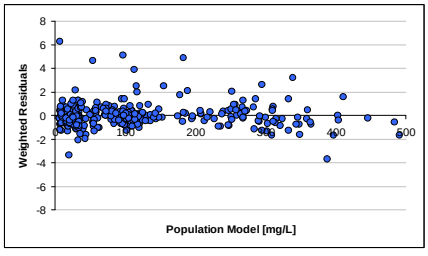

Figure 5: Weighted residuals in the population model

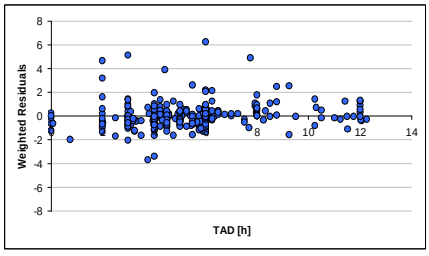

Figure 6: Weighted residuals over time after dose

Acknowledgements

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Conclusion

We could confirm the results from our previous study without observing significant differences in $Cl_{initial}$ and V between the two cohorts. The steeper increase in clearance in the standard dose group might be explained by a higher constant exposure of DMA.