Population pharmacokinetic analysis of high-dose oral busulphan for bone marrow transplant in adults and children

Carl Kirkpatrick[1], Stephen Duffull[1], Murray Barclay[2], Nigel Patton[3], Grant Moore[4], Matthew Doogue[2]

1. School of Pharmacy, University of Queensland, Australia
2. Department of Clinical Pharmacology, Christchurch Hospital, New Zealand
3. Haematology, Christchurch Hospital, New Zealand
4. Toxicology, Canterbury Health Laboratories, Christchurch, New Zealand

Introduction

- Busulphan is an alkylating agent used in high dose for bone marrow conditioning prior to transplantation
- Standard dose is 1mg/kg 6-hourly for 4 days, with target AUC proposed for efficacy and toxicity
- Initial non-compartmental analysis suggested a systematic change in AUC during treatment

Aim

- To develop a covariate model to assist the dosing of oral busulphan for bone marrow conditioning prior to transplantation in adults and children

Data

- 24 patients, 11 adults, 13 children (8F/16M) – Ethics Committee Approved
- 196 plasma drug concentrations over (up to) 3 occasions (0, 24/30, 72 hours)

	<16 years (mean ± sd)	> 16 years (mean ± sd)
Age (yrs)	5.6 ± 3.8	37.3 ± 11.4
Weight (kg)	24.2 ± 12.7	71.1 ± 13.5
Height (cm)	113 ± 28.1	172.4 ± 11.8
Serum Creatinine (mM)	0.036 ± 0.009	0.075 ± 0.021

Structural Model

- Model building performed using NONMEM (V) using FOCE with interaction with G77 compiler
- Base Model - 1 compartment oral model (ka, CL, V) with mixed error model
  - BSV and BOV (3 occasions) on Ka, CL and V
  - Parameter estimates similar to previous studies

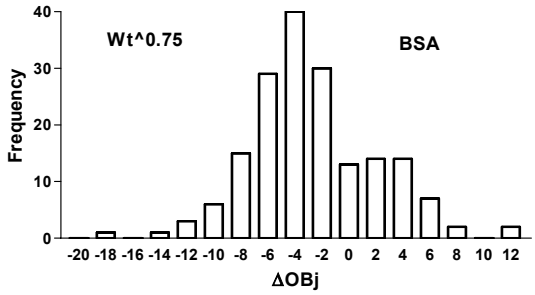
Covariate Model

- Best covariate for V was weight (WT)
- Two possible covariate models for CL
  - Weight^0.75 - allometric scaling eg CL= THETA(1)*(WT/median)^0.75
  - Body surface area (BSA) eg CL=THETA(1)*(BSA/1.9)
- Allometric model had a slightly lower objective function (OBj) (-3.5) compared with BSA
  - BSV similarly reduced for both models

Model Selection

- To assess best covariate model
  - 1000 non-parametric bootstrapped data sets generated
  - Both covariate models were fitted to each data set and the value of the objective function (OBj) under each model was recorded
  - Δ OBj between models computed, and density plotted to provide the pseudo-posterior probability of one model over another (see figure 1)
  - Density of the distribution of Δ OBj <0 was 0.75 indicating the allometric scaling model was preferred with a probability of 0.75 (or odds of 3)

Figure 1 – Density of Distribution of ΔOBj



Model Evaluation

POSTERIOR VISUAL CHECK (PVC)

- Given the large range of ages in the patient group, a visual check of the predictive capabilities of the model was undertaken via simulation in MATLAB®
  - The weight distribution of patients <16years and >16 years of age were calculated from the original population
  - 10,000 patients were simulated from each weight distribution, and dosed at 1mg/kg
  - Concentration-time profiles were predicted from the final covariate model with BSV and BOV
  - The 10th, 50th and 90th percentiles of the concentration-time profiles are shown at each of the dosing occasions (See figures 2 and 3)
  - The percentile curves were over-layed on the original data to see if any systematic model errors could be observed

Figure 2 - Age < 16 years

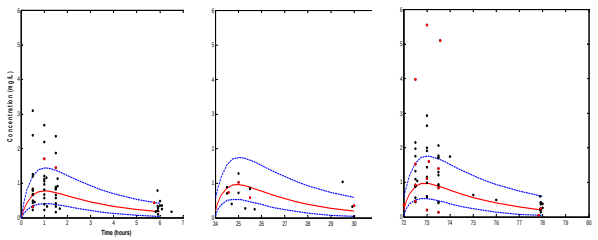
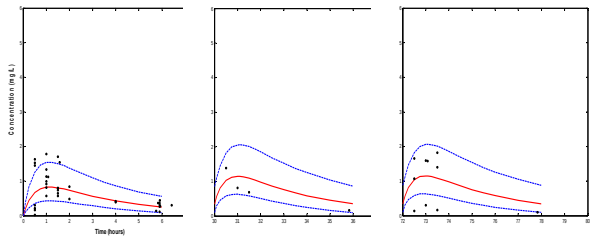


Figure 3 – Age > 16 years



Black dots (●) = patients dosed 1mg/kg. Red dots (●) = patients dose changed during treatment
Blue dashed line (---) = 10th and 90th percentile Red solid line (–) = 50th percentile

Discussion

- BOV was small (<15%) therefore a target concentration intervention approach would be applicable for busulphan
- A boot-strapped pseudo-posterior supported the allometric scaling model as indicated by initial reduction of OBj in NONMEM
- Final covariate model did appear to miss some peak concentrations particularly in the children