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

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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)

<table>
<thead>
<tr>
<th>&lt;16 years (mean ± sd)</th>
<th>&gt; 16 years (mean ± sd)</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>5.6 ± 3.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>24.2 ± 12.7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>113 ± 28.1</td>
</tr>
<tr>
<td>Serum Creatinine (mM)</td>
<td>0.036 ± 0.009</td>
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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
  - ∆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 ∆OBJ <0 was 0.75 indicating the allometric scaling model was preferred with a probability of 0.75 (or odds of 3)

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 <16 years 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

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