Busulfan TCI Audit and Model Evaluation

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Slide 2

Background

- Intravenous high dose busulfan is used for bone marrow conditioning prior to bone marrow transplant
- Target concentration intervention for busulfan is recommended in the FDA label (AUC method)
- Bayesian TCI has been in use at Auckland Starship and Auckland City hospital for all busulfan bone marrow conditioning since March 2012

Slide 3

Busulfan Audit

- Ethical approval from HDEC to conduct a clinical audit of busulfan use
- LabPlus (Auckland) performs all busulfan concentration measurements
- Laboratory scientists at LabPlus trained to use NextDose to enter demographic, dose and concentration data
- LabPlus provides NextDose report to clinical staff with future maintenance dose proposal
Audit Summary
69 Reports March 2012-Jan 2015

- **Target**
  - 4800 umol/L/min with dosing interval of 24 h (49 reports)
  - 2400 umol/L/min with dosing interval of 12 h (1 report)
  - 0.77 mg/L (10 reports)

- **Target Errors**
  - AUC 4800 umol/L/min with dosing interval of 2 h (8 reports)
  - Conc of 4800 umol/L (1182 mg/L) (1 report)

- **Documentation**
  - 13 clinical consultants
  - Clinical consultant not identified (27 reports)

TCI Model Evaluation

<table>
<thead>
<tr>
<th>Booth 2007</th>
<th>NextDose 2012</th>
<th>McCune 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 children, teenagers</td>
<td>67 infants, children, adults</td>
<td>1610 infants, children, adults</td>
</tr>
<tr>
<td>384 observations 3 occasions</td>
<td>371 observations 1 to 4 occasions</td>
<td>12,380 observations 1 to 3 occasions</td>
</tr>
<tr>
<td>1 compartment Empirical allometry Total body weight No maturation</td>
<td>1 compartment Theory based allometry Total Body weight Best guess maturation Post-menstrual age</td>
<td>2 compartment Theory based allometry Normal fat mass Estimated maturation Post-menstrual age Sex (V), Time (CL)</td>
</tr>
<tr>
<td>BSV + BOV No correlation</td>
<td>BSV + BOV BSV Correlation CL and V</td>
<td>BSV + BOV BSV &amp; BOV Correlation CL,V1,Q,V2 (full block)</td>
</tr>
</tbody>
</table>

Objective Function Value
MAXEVAL=0

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<tr>
<th>Booth 2007</th>
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</thead>
<tbody>
<tr>
<td>-489</td>
<td>-534</td>
<td>-387</td>
</tr>
</tbody>
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Total: 395 observations
1 occasion: 69 subjects
2 occasions: 10 subjects
3 occasions: 2 subjects
4 occasions: 1 subject


"true" clearance for each subject in each model was estimated from the empirical Bayes estimate using all occasions (Occ_all). Best prediction was based on performance of each model prediction of occasion 1 clearance (Occ1).
Summary

- Audit
  - NextDose usable by clinical laboratory staff without specialist TCI guidance
  - 1 serious dose error on Nextdose report due to mistaken entry of target AUC value with conc units
  - 8 moderate errors on NextDose report due to mistaken dosing interval

- Model Evaluation
  - McCune 2014 model more complex but overall better prediction of observed concentrations and future dosing