Application of the optimal design approach to improve pre-transplant drug monitoring for cyclosporine

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Procedures in Finland during paediatric renal transplantation

Transplantation

CyA iv test
CyA po test

CyA iv therapy
CyA po therapy

Knowledge gained used to individualize therapy initiation
Previous design

- 162 IV patients & 89 PO patients (77 with both) were collected (1988-2005)
  - During this time; individual models were used to predict 1st iv and 1st oral post transplant dose

- In 2007 a Population PK model was published by Fanta et al*

Aim

• Reduce and optimise the pre-transplant cyclosporine monitoring design for an analysis of individual parameters which used priors from the population model

• Work within clinical restrictions
Clinical Restrictions

- Maximum of 3 samples per dose
- Maximum total cyclosporine dose (IV+PO) of 10 mg/kg
- Maximum infusion rate for IV: 0.75 mg/kg/h
- Fit both doses IV+PO within 8 hour time limit
What can we optimize on?

- Sampling times IV, PO
- Doses IV, PO
- Durations of infusion for IV
- Start of second dose
- IV first then PO and vice versa
Methods used

• 8 individual parameters (EBEs) transformed to fixed effect parameters
• Continuous distributions (variances of parameter distributions) to represent prior information on the *individual level*
• Discrete distributions for ED-sampling
• Optimization of all design variables simultaneously
• WT as covariate, Doses were optimized as mg/kg

• $ED_{s}$-optimality used for following parameter subsets of interest:
  – EBEs of CL and F only
  – EBSs of all 6 parameters
  – EBEs of all 6 parameters and 2 of the RUV (eta on eps)

• Sampling windows
• Efficiency loss compare to previous rich design

• Optimization was performed in PopED v.2
Methods
ED samples from discrete distributions

• Optimization across a discrete distribution of 77 individual parameter vectors

• Includes correlation between parameters

• Reflect future patients distribution, however bias to previous patients

• $\eta$-Shrinkage was on average 6%
Methods
Focus on some parameters (CL & F)

- Focus on CL and F as during chronic dosing
  - Average concentration = Dose rate \times \frac{F}{CL}

Assume all other known
Methods
Focus on some parameters (CL & F)

- Focus on CL and F as during chronic dosing
  - Average concentration = Dose rate * F / CL

<table>
<thead>
<tr>
<th>CL</th>
<th>F</th>
<th>V3</th>
<th>Q3</th>
<th>V2, Q4, V4</th>
<th>Ka</th>
<th>RUV IV</th>
<th>RUV PO</th>
</tr>
</thead>
</table>

Not of interest
Methods
ED$_s$ - optimality

\[
ED_s = \max \left( E \left[ \left| \frac{\text{FIM}_{\text{total}}}{\text{FIM}_{\text{uninteresting}}} \right| \right] \right)
\]

- The smaller the $|\text{FIM}_{\text{uninteresting}}|$ the larger the $D_s$

- Keeps correlation between all parameters of the model compared to not including certain parameters in the FIM calculation (fixing parameters)

Results

Designs optimized for CL & F

<table>
<thead>
<tr>
<th>Sampling Times</th>
<th>IV PO design</th>
<th>PO IV design</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>2.33</td>
<td>3.04</td>
</tr>
<tr>
<td></td>
<td>2.81</td>
<td>7.68</td>
</tr>
<tr>
<td></td>
<td>3.98</td>
<td>8.00</td>
</tr>
<tr>
<td>PO</td>
<td>4.71</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>8.00</td>
<td>2.96</td>
</tr>
<tr>
<td></td>
<td>8.00</td>
<td>2.96</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other design variables</th>
<th>IV PO design</th>
<th>PO IV design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose IV (mg/kg)</td>
<td>1.05</td>
<td>3.00</td>
</tr>
<tr>
<td>Dose PO (mg/kg)</td>
<td>8.95</td>
<td>7.00</td>
</tr>
<tr>
<td>Infusion time</td>
<td>1.41</td>
<td>4.00</td>
</tr>
<tr>
<td>Infusion Rate</td>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
<td>Time of second dose</td>
<td>4.00</td>
<td>3.04</td>
</tr>
</tbody>
</table>
Results
Comparison to previous designs

- Showing the individual expected precisions (CVs) obtained from PopED

<table>
<thead>
<tr>
<th></th>
<th>Original design Individual</th>
<th>Optimal design</th>
<th>Priors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IV PO design</td>
<td>PO IV design</td>
</tr>
<tr>
<td>V3</td>
<td>26.2%</td>
<td>41.1%</td>
<td>40.1%</td>
</tr>
<tr>
<td>Q3</td>
<td>18.0%</td>
<td>30.2%</td>
<td>31.0%</td>
</tr>
<tr>
<td>V2 Q4 V4</td>
<td>53.9%</td>
<td>34.7%</td>
<td>37.9%</td>
</tr>
<tr>
<td>CL</td>
<td></td>
<td>6.7%</td>
<td>9.3%</td>
</tr>
<tr>
<td>KA</td>
<td>21.1%</td>
<td>19.4%</td>
<td>19.0%</td>
</tr>
<tr>
<td>F</td>
<td>10.8%</td>
<td>13.5%</td>
<td>13.5%</td>
</tr>
<tr>
<td>EPS RUV IV</td>
<td>20.5%</td>
<td>29.6%</td>
<td>29.6%</td>
</tr>
<tr>
<td>EPS RUV PO</td>
<td>22.5%</td>
<td>32.1%</td>
<td>32.1%</td>
</tr>
</tbody>
</table>
• Comparison of the efficiency of the reduced optimal vs. the Rich Design Individual

\[
\text{Efficiency} = \left( \frac{|FIM_{\text{total}}|}{|FIM_{\text{uninteresting}}|} \right)^{1/s}_{\text{optimal reduced design}} \div \left( \frac{|FIM_{\text{total}}|}{|FIM_{\text{uninteresting}}|} \right)^{1/s}_{\text{original full design}}
\]

• Efficiency \( \sim 47\% \)
Results
Sampling and Dose windows

- Defining windows and then calculating the efficiency for 100 samples from the windows

- Efficiency reduction of 5-10% when applying sampling windows, further 3% efficiency reduction with dose windows
Conclusions

• A new method were developed for optimization of EBEs with inclusion of prior information

• Multiple design variables were optimized simultaneously

• Reduction to 6 blood samples within 8 hours possible including constrains and sampling/dose windows for clinical practicality

• CVs on the EBEs for CL and F could be reduced on average by 60% compared to the Prior information

• The gain of performing the Rich Design compared to the optimal reduced designs with regards to the precision of the parameters is small
Acknowledgements

Kalle Hoppu