Comparing Methods for Once Daily Tobramycin Exposure Predictions in Children with Cystic Fibrosis

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Cystic fibrosis (CF) & Once-daily tobramycin treatment

- Tobramycin – antibiotic of choice for pulmonary exacerbation in CF
- Concentration-dependent killing
- Side effects – nephrotoxicity and ototoxicity
- Once-daily approach preferred
- Therapeutic drug monitoring (TDM) necessary
Common TDM methods for Tobramycin

- Nomogram method
  - TG nomogram, Massie nomogram
- Linear regression method
- Computerised Bayesian forecasting method
  - TCIWorks, DoseMe
Nomogram

Next dose (mg)

\[
= \frac{\text{Target concentration at sampling time (mg/L)}}{\text{Measured concentration at sampling time (mg/L)}} \times \text{Initial Dose}
\]
Linear regression (LR) analysis

- $AUC_{0-24}$ calculated via linear regression from $C_1$ and $C_2$
- Assumption of 1 compartment distribution model
- Extrapolate to $C_{\text{max}}$, $C_{\text{min}}$
- Can be done with a calculator or Excel spreadsheet

Next dose = \[
\frac{\text{target } AUC \times \text{previous dose}}{AUC \text{ of previous dose}}
\]
Bayesian Forecasting

• Therapeutic Guidelines (TG) in Australia recommend computerized methods (e.g. Bayesian forecasting) for aminoglycoside dose individualization since 2010

• *A priori* population PK model and *a posteriori* data to calculate individual PK parameters for dosage adjustment recommendations

• Bayesian methods modify initial, population-derived PK parameters using patient’s own dosing history, demographic data and concentration-time measurements to predict individual PK parameters
Bayesian Forecasting

TCIWorks, DoseMe

- 2 compartment model
- Allometric scaled WT on CL & V
- Only CF children


- 2 compartment model
- WT on CL, V1, Q, V2
- SCR on CL
- Age on CL
- Sex on CL & V
- Children and adults, CF and non-CF

Aim

- To compare the three common monitoring methods for dose individualization of IV tobramycin in CF children
  - in terms of their predictive performances
  - their dose recommendations
- Evaluate current practice using the linear regression method
Patients and data collection

• Ethics approval - Royal Children’s Hospital, Brisbane and The University of Queensland

• Retrospective data
  • CF children who received more than 1 IV tobramycin treatment course between 1999-2008
  • Had two tobramycin concentration within one dosing interval
    (C₁ obtained at ~2 hours post-dose & C₂ 6-14 hours post-dose)
Method comparison

**Data**
- Paired tobramycin concentrations ($C_1$ and $C_2$)
- Patient demographics, other clinical information

**TDM Methods**
- TG nomogram
- Massie nomogram
- Linear regression method
- TCIWorks
- DoseMe

**Comparison**
- New dose recommendations
- Targets: median nomogram line, AUC=100 mg.h/L
- Estimated drug exposure
- Individual PK parameters
- Compared to true concentrations
Results - Data

• Total 707 paired plasma tobramycin concentration (=sets) collected from 173 CF patients

• Within one treatment course:
  396 sets of concentrations = first sampling occasion,
  217 follow-up sets = second sampling occasion
  76 follow up sets = third sampling occasion
  16 follow up sets = fourth sampling occasion

• 442 course in total
  78 patients had 1 course, 45 patients had 2 courses, 23 patients had 3 courses, 11 patients had 4 courses, 4 Patients had 5 courses, 5 patients had 6 courses, 4 patients had 7 courses, 1 patient had 8/12/15 courses, 3 patients had 9 courses, 2 patients had 11 courses
## Results - Patient Demographics

<table>
<thead>
<tr>
<th>Patient Demographics</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>11.76 ± 5.26</td>
<td>1.0 – 22.0</td>
</tr>
<tr>
<td>Males/Female (%)</td>
<td>54/46</td>
<td>-</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>129.3 ± 31.5</td>
<td>54.6 – 188.0</td>
</tr>
<tr>
<td>Total Body Weight (kg)</td>
<td>32.2 ± 17.6</td>
<td>3.8 – 92.0</td>
</tr>
<tr>
<td>Lean Body Weight (kg)*</td>
<td>24.7 ± 18.9</td>
<td>3.7 – 54.0</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>0.09 ± 0.015</td>
<td>0.030 – 0.104</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)**</td>
<td>109.2 ± 29.4</td>
<td>46.8 – 181.3</td>
</tr>
</tbody>
</table>

*Lean body weight calculated using the equation by Janmahasatian et. al.

**Creatinine clearance calculated using the Schwartz formula
Results - Current clinical practise

- Initial starting dose of $10.11 \pm 2.42\text{mg/kg}$
- $t_1 = 2.1 \pm 0.4\text{h}$ $t_2 = 6.2 \pm 0.6\text{h}$ post-dose
- $C_1 = 16.6 \pm 5.7\text{mg/L}$ $C_2 = 2.9 \pm 1.6\text{mg/L}$

- 210 single samples, 6 patients excluded - unsuitable for LR method and excluded from the comparison
  - 135 $C_2$ only, 75 $C_1$ only samples
  - no BQL samples
  - 63 times only one sample after the first dose taken and in 20 cases resampling occurred the next day
## Results - Current clinical practise

<table>
<thead>
<tr>
<th>AUC&lt;sub&gt;0-24&lt;/sub&gt; (mg.h/L)</th>
<th>First set (n=398)</th>
<th>Second set (n=215)</th>
<th>Third set (n=76)</th>
<th>Fourth set (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;80</td>
<td>48%</td>
<td>31%</td>
<td>32%</td>
<td>31%</td>
</tr>
<tr>
<td>80-100</td>
<td>25%</td>
<td>38%</td>
<td>33%</td>
<td>32%</td>
</tr>
<tr>
<td>100-125</td>
<td>21%</td>
<td>24%</td>
<td>26%</td>
<td>31%</td>
</tr>
<tr>
<td>&gt;125</td>
<td>6%</td>
<td>7%</td>
<td>9%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Percentage of patients achieving various AUC<sub>0-24</sub> targets based on the application of the linear regression method on subsequent sampling occasions (sets)

- Set = sets of C<sub>1</sub> and C<sub>2</sub> samples within one treatment course
- Target AUC<sub>0-24</sub> = 100mg.h/L
- ~50% patients only reach AUC > 80 mg.h/L after initial dose
- 5 patients still < 80 mg.h/L after three dose adjustments
Results - Recommended next doses (mg/kg)

- a – statistically different from all others
- b – statistically different from TCI & DM using a one-way ANOVA test followed by Tukey’s Test in SPSS, \( p \leq 0.05 \)

Initial starting dose: 10.11 mg/kg
## Results - AUC and Dose

- AUC predictions only for Linear regression (LR), TCIWorks and DoseMe (DM)
- mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>TG C₂</th>
<th>Massie C₁</th>
<th>LR C₁ &amp; C₂</th>
<th>TCI C₁ &amp; C₂</th>
<th>TCI C₁</th>
<th>TCI C₂</th>
<th>DM C₁ &amp; C₂</th>
<th>DM C₁</th>
<th>DM C₂</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC₀⁻²₄ (mg.h/L)</strong></td>
<td>-</td>
<td>-</td>
<td>87.15 ± 28.3</td>
<td>84.1 ± 18.8</td>
<td>86.9 ± 19.0</td>
<td>84.3 ± 18.1</td>
<td>93.8 ± 27.3</td>
<td>98.3 ± 39.3</td>
<td>94.9 ± 29.0</td>
</tr>
<tr>
<td><strong>Next Dose (mg/kg)</strong></td>
<td>27.6 ± 22.3</td>
<td>14.4 ± 5.2</td>
<td>13.5 ± 5.3</td>
<td>13.1 ± 3.3</td>
<td>12.6 ± 2.8</td>
<td>13.0 ± 3.1</td>
<td>12.3 ± 4.6</td>
<td>12.0 ± 4.6</td>
<td>12.2 ± 4.7</td>
</tr>
</tbody>
</table>
## Results - Predictive Performance

- Comparing predicted concentrations to observed “true” tobramycin concentrations
- TCIWorks and DoseMe show acceptable results regarding bias and precision using both samples, but also just utilising one sample

<table>
<thead>
<tr>
<th></th>
<th>TCI C1 &amp; C2</th>
<th>DM C1 &amp; C2</th>
<th>TCI C1</th>
<th>TCI C2</th>
<th>DM C1</th>
<th>DM C2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MPE %</strong></td>
<td>6.0</td>
<td>-2.8</td>
<td>-3.1</td>
<td>-</td>
<td>-2.2</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(-44.8 – 38.4)</td>
<td>(-38.6 – 18.6)</td>
<td>(44.1 - -39.0)</td>
<td></td>
<td>(-37.7 – 19.5)</td>
<td></td>
</tr>
<tr>
<td><strong>RMSE %</strong></td>
<td>18.2</td>
<td>8.1</td>
<td>18.3</td>
<td>-</td>
<td>6.2</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(0.6 – 49.2)</td>
<td>(0.7- 39.3)</td>
<td>(0.9-49.0)</td>
<td></td>
<td>(0.0 – 38.8)</td>
<td></td>
</tr>
<tr>
<td><strong>C2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MPE %</strong></td>
<td>-2.6</td>
<td>-2.3</td>
<td>-1.4</td>
<td>-</td>
<td>-2.5</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(-45.3 – 26.5)</td>
<td>(-35.4 – 20.8)</td>
<td>(-44.4 - 27.6)</td>
<td></td>
<td>(-36.1– 17.1)</td>
<td></td>
</tr>
<tr>
<td><strong>RMSE %</strong></td>
<td>13.9</td>
<td>7.1</td>
<td>15.4</td>
<td>-</td>
<td>6.0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(0.5 – 47.3)</td>
<td>(0.0 – 36.4)</td>
<td>(0.6 – 46.0)</td>
<td></td>
<td>(0.0 – 36.1)</td>
<td></td>
</tr>
</tbody>
</table>
Results - Predicting PK parameters

- Only for Linear regression, TCIWorks and DoseMe using both C1 & C2
- Reported as mean (SD)

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>LR</th>
<th>TCI</th>
<th>DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/h)</td>
<td>3.83 ± 1.78</td>
<td>3.7 ± 1.5</td>
<td>3.5 ± 1.5</td>
</tr>
<tr>
<td>CL (L/kg/h)</td>
<td>0.13 ± 0.05</td>
<td>0.13 ± 0.03</td>
<td>0.12 ± 0.04</td>
</tr>
<tr>
<td>Vd (L)</td>
<td>9.18 ± 4.92</td>
<td>8.3 ± 4.6</td>
<td>7.8 ± 4.3</td>
</tr>
<tr>
<td>Vd (L/kg)</td>
<td>0.31 ± 0.13</td>
<td>0.26 ± 0.02</td>
<td>0.26 ± 0.10</td>
</tr>
<tr>
<td>AUC₀-2₄ (mg.h/L)</td>
<td>87.5 ± 28.3</td>
<td>84.1 ± 17.8</td>
<td>93.8 ± 27.3</td>
</tr>
<tr>
<td>Cₘₐₓ (mg/L)</td>
<td>34.8 ± 15.1</td>
<td>35.7 ± 9.1</td>
<td>40.4 ± 18.5</td>
</tr>
<tr>
<td>Cₘᵦₙ (mg/L)</td>
<td>0.01 ± 1.62</td>
<td>0.004 ± 0.01</td>
<td>0.02 ± 0.06</td>
</tr>
</tbody>
</table>

Pharmacometrics Group
School of Pharmacy, The University of Queensland
Summary - Practicalities

• Validity of the nomogram depends on the patient of interest being similar to the population used to create the nomogram.
• CF patients are different physiologically to other patients populations – resulting in sub-therapeutic concentrations when plotted against the TG nomogram.
• Signal-to-noise ratio too small at late sample point to be used for dose adjustment in the TG nomogram.
• Newer tobramycin model could not be implemented into current available TCIworks version.
Conclusion

• TG nomogram recommended statistically different tobramycin doses

Comparing 3 Methods of Monitoring Gentamicin Concentrations in Patients With Febrile Neutropenia

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• If limited computer or internet access, the linear regression method should be considered first, followed by the Massie nomogram

• Preliminary results show that predictive performance of Bayesian forecasting methods using 1 sample not different from using 2 samples
Acknowledgements

• **Results still be extended:**
  • checks for data entry mistakes are performed currently
  • Analysis of Bayesian methods for one sample use still to be finalised
  • Changes of predicted performance within a treatment course evaluated

• **Dr. Robert McLeay**
  for providing access and implementation of the latest tobramycin pharmacokinetic model into the DoseMe software.
Questions