Comparing Dosage Adjustment Methods for Once Daily Tobramycin in Paediatric and Adolescent Patients with Cystic Fibrosis

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Fig. 1S: Calculations for log-linear regression analysis

\( C_1 \) = first measured serum concentration (mg/L)
\( C_2 \) = second measured serum concentration (mg/L)
\( t_1 \) = time at which the first serum concentration was measured (h)
\( t_2 \) = time at which the second serum concentration was measured (h)
\( C_{\text{end}} \) = concentration at the end of the infusion (theoretical maximum concentration) (mg/L)
\( t_{\text{max}} \) = time at the end of the infusion (h)
\( t_{\text{min}} \) = 24 hours post-dose (theoretical minimum concentration) (h)
\( t_{\text{end}} \) = end of infusion (h)
\( k_e \) = elimination rate constant (h\(^{-1}\))
\( CL \) = Clearance (L/h)
\( Dose \) = Dose given (mg)
\( V_d \) = Volume of Distribution (L)

\[
k_e = \frac{\ln(C_1) - \ln(C_2)}{t_2 - t_1} \quad (1S)
\]

\[
C_{\text{end}} = \frac{C_1}{e^{-k_e(t_1-t_{\text{end}})}} \quad (2S)
\]

\[
C_{24} = C_2 \times e^{-k(24-t_2)} \quad (3S)
\]

\[
AUC_{0-24} = AUC_{(t_{\text{end}}-24)} + AUC_{(t_0-t_{\text{end}})}
\]

\[
AUC_{0-24} = \frac{(C_{\text{end}}-C_{24}) + (t_{\text{end}}\times C_{\text{end}})}{k} \quad (4S)
\]

\[
CL = \frac{Dose}{AUC} \quad (5S)
\]

\[
V_d = \frac{CL}{k} \quad (6S)
\]
Fig. 2S: Bland-Altman plots showing the difference in recommended doses (mg/kg) when estimated using DoseMe (DM) and TCIWorks (TCI) (top panel), log-linear regression method (LR) and TCIWorks (middle panel) and log-linear regression method and DoseMe (bottom panel) versus the average dose (mg/kg) difference between the methods, when both concentrations of each set (left panel), only the first concentration measurement (middle panel) or only the second concentration measurement within the same dosing interval (right panel) were used within the Bayesian forecasting programs. The solid line represents no difference between methods, the dashed line represents the median difference and the two dotted lines the 2.5th and the 97.5th percentile difference.
### Table 1S: Populations pharmacokinetic models and parameters used in the Bayesian Forecasting software programs TCIWorks and DoseMe for Tobramycin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TCIWorks</th>
<th>DoseMe</th>
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<tbody>
<tr>
<td>Parameter Value</td>
<td>Value (BSV (CV %))</td>
<td>Value (BSV (CV %) + BOV (CV %))</td>
</tr>
<tr>
<td>Structural model</td>
<td>2 compartment distribution model</td>
<td>2 compartment distribution model</td>
</tr>
<tr>
<td>Clearance (L/h/70 kg)</td>
<td>6.37 (11.7)</td>
<td>Females: 8.1 (25.9 + 12.7)</td>
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<td></td>
<td></td>
<td>Males: 9.4 (25.9 + 12.7)</td>
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<tr>
<td>Central volume of distribution (L/70 kg)</td>
<td>18.7 (11.66)</td>
<td>Females: 20.1 (15.2)</td>
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<td></td>
<td></td>
<td>Males: 25.1 (15.2)</td>
</tr>
<tr>
<td>Inter-compartmental clearance (L/h)</td>
<td>0.39</td>
<td>1.5 (L/h/70kg) (41.8)</td>
</tr>
<tr>
<td>Peripheral volume of distribution (L)</td>
<td>1.39 (41.95)</td>
<td>10 (L/70kg) (58.5)</td>
</tr>
<tr>
<td>Proportional residual error (%)</td>
<td>19.0</td>
<td>20.4</td>
</tr>
<tr>
<td>Covariate relationships included</td>
<td>WT allometrically scaled on CL and Vc</td>
<td>LBW on CL, Q, Vc, Vp SEX on CL, Vc</td>
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<tr>
<td></td>
<td></td>
<td>Age on CL</td>
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<tr>
<td></td>
<td></td>
<td>SCR on CL</td>
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</tbody>
</table>

BSV - between subject variability  
BOV - between occasion variability  
CL - clearance  
Vc - central volume of distribution  
Vp - peripheral volume of distribution  
Q – inter-compartmental clearance  
WT - total body weight  
LBW – lean body weight by Janmahasatian et al.  
SEX - sex of the patient  
AGE - age of the patient  
SCR – serum creatinine concentration