Individualization of Cefuroxime Dosage using Pharmacodynamic targets, MIC distributions and Minimization of a Risk Function

Anders Viberg, Otto Cars, Mats O. Karlsson and Siv Jönsson

Division of Pharmacokinetics and Drug Therapy
Department of Pharmaceutical Biosciences
Uppsala University
Aim

To further develop the methodology of estimating dosing strategies

and

To develop individualized dosing strategies for cefuroxime
Cefuroxime

- Cephalosporin
- Intravenous administration
- Renal elimination
General drug treatment target

- As many patients as possible should be given effective treatment
- As few patients as possible should have side-effects
Drug treatment target for cefuroxime

Craig, Clin Infect Dis 26:1-10
Drug treatment risk function for cefuroxime
Drug treatment risk function for cefuroxime
Risk function minimized during dosing estimation
Establishing dosing strategies

- Target population
- Estimate the dosing
- Evaluate the dosing
Target population characteristics

- Cefuroxime population PK model to simulate a large population
- Empirical distribution of covariates reflecting target population
  - CLcr covariate for clearance
  - WT covariate for V1
Estimation of dosing

In this example
- Fixed dose sizes
- Estimating dosing intervals and CLcr cut-offs
- Varying number of dosing categories

<table>
<thead>
<tr>
<th>Clcr (mL/min)</th>
<th>Dose (mg)</th>
<th>Dosing interval (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>750</td>
<td>24</td>
</tr>
<tr>
<td>20-40</td>
<td>750</td>
<td>12</td>
</tr>
<tr>
<td>40-80</td>
<td>750</td>
<td>8</td>
</tr>
<tr>
<td>&gt; 80</td>
<td>1500</td>
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## Estimated dosing

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<tr>
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</thead>
<tbody>
<tr>
<td>≤ 50</td>
<td>5.28</td>
<td>≤ 50</td>
<td>12.04</td>
<td>≤ 50</td>
<td>12.04</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>30-80</td>
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<tr>
<td></td>
<td>&gt; 80</td>
<td>&gt; 50</td>
<td>5.29</td>
<td>&gt; 70</td>
<td>4.19</td>
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|               |                      |  > 80         | 5.29                |  > 70         | 4.19                |

### Which is the best???
Evaluating the estimated dosing

- Each individual was assigned one MIC value from each MIC distribution
- Deviations from the target using the MIC distributions was graphically analyzed
Evaluating with respect to *E. coli*

- **4 dosing categories**
- **3 dosing categories**
- **2 dosing categories**
Estimated dosing with respect to *S.pneumoniae*

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<td>&gt; 40</td>
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48 hour dosing interval
Expanded risk function

Risk

Time below MIC = 4 h
Time below MIC = 6 h
Time below MIC = 8 h
Time below MIC = 10 h

%\%T_{>MIC}

Risk

Time below MIC = 4
Time below MIC = 6
Time below MIC = 8
Time below MIC = 10

Drug in excess
Estimated dosing with respect to *S.pneumoniae*

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Evaluating with respect to \( S.pneumoniae \)

Original risk function

Expanded risk function
Dosing strategies

### E.coli

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### S.pneumoniae

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Summary

• Illustration of how individualized dosing strategies can be estimated using a combined risk function
• Different dosing strategies for cefuroxime might be used for different infecting species
• An example of how MIC distributions can be used in drug development