Population pharmacokinetics of unbound temocillin in paediatric patients requiring antibiotic prophylaxis following hepatic transplantation

Perrin Ngourro Pokem1, Xavier Stéphénon2, Isabelle K. Delattre1, Dimitri Van der Linden1, Christina Mark2, Arnaud Capron3, Pierre Wallenmuller3, Paul M Tulkens1, Etiennne Soki1, François Van Bambeke4

1Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium; 2Cliniques Universitaires St Luc, Université catholique de Louvain, Brussels, Belgium; 3Laboratoire de Recherches cliniques, Université Paris 13, Bobigny, 93177, France; 4ISTR, Université catholique de Louvain, Brussels, Belgium.

Background and Aims

- Temocillin (6α-methoxy-ticarcillin), is a β-lactam antibiotic active on Gram (-) bacteria (except most isolates of Pseudomonas aeruginosa [1]), including strains producing extended-spectrum β-lactamases (ESBL) and some carbapenemases [2].

Materials and Methods

- Study design and Investigational Plan
  - Single-center, open-label, non-randomized study.
  - 14 liver transplant male or female children (12-36 months old) who were infused with 25mg/kg temocillin over 30 minutes every 12 hours, one day before (day 1) and five days (days 5) after transplantation.
  - First blood samples were drawn on day +1 (dose 1 or 2) and second one among doses 3 to 9 sampling times were 0.5, 2, 4, 8 and 12 hours after dose administration.

- Population pharmacokinetic modelling
  - Population PK modelling was carried out using the nonlinear mixed effects modelling program NONMEM (version V) [1]

- Reference

  References


Discussion and Conclusions

- TMO shows bi-compartmental pharmacokinetics.
- In spite of the large variability among these patients, the data suggested that current licensed dosage regimen is suboptimal for MICs >4 mg/L or PD targets of 70 or 100% fT>MIC or 8 mg/L, which may be required in this fragile patient population.
- Further analysis are needed
  - Search and test relevant confounding factor
  - Full validation of the model
  - Evaluate the Probability of Target Attainment (PTA)
  - Use model to simulate and proposed optimized dosing regimen.

Results

- Bi-compartmental model with linear elimination best fitted unbound TMO concentrations.

- Goodness-of-fit plots of the final model of TMO concentrations.

- Final population pharmacokinetic parameter estimates:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (±% RSE)</th>
<th>Interindividual (±% RSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1 (L/kg)</td>
<td>0.82 (±22.7%)</td>
<td>48.0% (±60.9%)</td>
</tr>
<tr>
<td>V2 (L/kg)</td>
<td>1.57 (±48.0%)</td>
<td>22.7% (±48.0%)</td>
</tr>
<tr>
<td>CL (L/h/kg)</td>
<td>0.10 (±64.5%)</td>
<td>64.5% (±64.5%)</td>
</tr>
<tr>
<td>V1/V2</td>
<td>0.54 (±22.7%)</td>
<td>30.0% (±60.9%)</td>
</tr>
<tr>
<td>CL/V1</td>
<td>0.10 (±48.0%)</td>
<td>64.5% (±64.5%)</td>
</tr>
<tr>
<td>V1/V2/CL</td>
<td>0.00 (±100%)</td>
<td>100.0% (±100%)</td>
</tr>
</tbody>
</table>

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1Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium; 2Cliniques Universitaires St Luc, Université catholique de Louvain, Brussels, Belgium; 3Laboratoire de Recherches cliniques, Université Paris 13, Bobigny, 93177, France; 4ISTR, Université catholique de Louvain, Brussels, Belgium.

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The dashed grey lines present the 2.5th and 97.5th percentiles of the observed data, and the solid grey line the median of observed data. The dashed black lines present the 2.5th and 97.5th percentiles of the simulated data, and the solid black line depicts the median of simulated data. The dashed grey lines are the observed concentrations, less than 5% of observed values and 95% of simulated concentrations.