**Using modeling and simulation to design and evaluate dosing strategies for temocillin in haemodialysis patients**

AC Miranda Bastos (1,2), SJ Vandecasteele (3), A Capron (4), PM Tulken (1), A Spinewine (2), F Van Bambeke (1)


**Background and Objectives**

- Temocillin is an anti-Gram-negative β-lactam active against many ESBL-producing Enterobacteriaceae but with limited population pharmacokinetics data on patients undergoing haemodialysis.
- Current dosing recommendations:[1] Haemodialysis regimen | Temocillin dose
  - every 24h | 500 mg
  - every 48h | 1000 mg

The purpose of this study was to develop a joint PK model of total and unbound temocillin serum concentrations in this patient population.

This model was also used to design and evaluate a dosing regimen aiming at a 90% probability of target attainment, i.e. unbound concentrations at least 40% of the interdialytic concentration above the largest minimal inhibitory concentration (40% T > MIC) of the main susceptible organisms (≤16mg/L).

**Methods**

- Single-center, open-label, non-randomized study
- 16 patients were administered a dose of 1, 2, or 3g of temocillin (total of 61 doses) followed by an interdialytic period (off-dialysis) of 20, 44, or 68h, respectively, and dialysis period of 4h.
- A nonlinear mixed effects model was fitted, taking both total and unbound temocillin concentrations from 429 serum samples into account.
- A 10,000-subject Monte Carlo simulation was conducted to determine the required dose to achieve 90% probability of target attainment over a wide range of patients’ weights (50-100kg).
- Data analyses were performed using NONMEM 7.3, Pirana, Pan and R.

**Results**

![Image](https://via.placeholder.com/150)

**Final PK parameter estimates**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (RSE %)</th>
<th>Bootstrap median (95% CI)</th>
<th>IIV / IOV CV% (RSE%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V1 (L/70kg)</td>
<td>32.7 (10.1)</td>
<td>23.4 (20.7 - 29.0)</td>
<td>38.1 (16.6)</td>
</tr>
<tr>
<td>V2 (L/70kg)</td>
<td>20.7 (10.5)</td>
<td>22.0 (18.2 - 26.4)</td>
<td>31.0 (22.9)</td>
</tr>
<tr>
<td>Q(L/70h/L)</td>
<td>4.1 (5.6)</td>
<td>4.1 (3.4 - 4.8)</td>
<td>-</td>
</tr>
<tr>
<td>Ka(T/L)</td>
<td>7.99 (17.4)</td>
<td>8.0 (5.5-10.6)</td>
<td>-</td>
</tr>
<tr>
<td>Vm(T/mg/70h/L)</td>
<td>411 (73)</td>
<td>258 (117-474)</td>
<td>47.4 (19.1)</td>
</tr>
<tr>
<td>Ke (L/mL)</td>
<td>253 (87.7)</td>
<td>143.8 (80.3-301.9)</td>
<td>38.1 (16.6)</td>
</tr>
<tr>
<td>Ke (mg/mL)</td>
<td>34.2 (21.2)</td>
<td>37.2 (24.2 - 58.4)</td>
<td>81.7 (21.4)</td>
</tr>
<tr>
<td>R(Vm/mL)</td>
<td>117 (12.7)</td>
<td>142.8 (106.3-159.4)</td>
<td>42.2 (26.2)</td>
</tr>
</tbody>
</table>

**Residual variability**

- Prop. Error CV%: 22.9 (18.9) | 22.5 (18.4 - 26.1)
- unbound conc.
- Prop. Error CV%: 18.0 (19.3) | 17.4 (13.8 - 19.7)
- total conc.

**Dose finding studies per dialysis regimen**

Required temocillin dose to achieve a PKPD target of 40% T > MIC as a function of body weight with 90% probability for a 24h (a), 48h (b, c) and 72h (d, e, f, g) interdialytic regimen. The simulated dosage schedule indicated in the respective graph was repeated 4 times.

**Simulations, probability of target attainment and PKPD breakpoints**

![Image](https://via.placeholder.com/150)

**Typical dialysis and dosing regimen**

- **Dosing table**
  - Week 1: 750 mg 1st dose, 750 mg 2nd dose (24h later)
  - Week 2: 1000 mg 1st dose, 1000 mg 2nd dose (24h later)
  - Week 3: 1500 mg 1st dose, 1500 mg 2nd dose (24h later)

**Mechanistic final PK model**

- **Albumin**
  - Patient Clearance
  - Dialysate Clearance
  - Intercompartmental clearance

**Conclusion**

A joint PK model of total and unbound serum concentrations described the time course of temocillin in patients undergoing haemodialysis. Off-dialysis was best described by a two-compartment model, non-linear binding to albumin (Langnuir model) and mixed order elimination. Dialysis clearance was best described by Michaelis equation. [2]

The prediction ability of the model decreases after approximately 130h. This likely reflects the fact that there are few patients (less than half) that are followed up for longer that amount of time.

Model-based simulations suggested a new temocillin dosing regimen for patients undergoing intermittent haemodialysis, in order to maintain drug concentrations over a MIC ≤ 16 mg/L, for at least 40% of the dosing interval. The typical thrice weekly haemodialysis regimen used in this study (regimen K) shows that patients would only be adequately treated (40% T > MIC) for a MIC ≤ 8mg/L.

Future clinical trials are warranted to confirm these results.

**References**


This poster will be made available for download after the meeting: http://www.facs.ucl.ac.uk/posers/2016
