Temocillin 6g daily in critically ill patients: continuous infusion vs. conventional administration

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TEMOCILLIN

- 6-α-methoxy-ticarcillin
- Spectrum directed only against Gram negative bacteria without non-fermenters (*Pseudomonas aeruginosa*, *Acinetobacter* spp.)
- Active against all producers of β-lactamase(s) including ESBL and AmpC
- Indications
  - Urinary tract infections
  - Gram negative nosocomial infections (LRTI, IAI, bacteremia, …)
6g vs 4g

- Usual posology is 4g per day

- PK/PD parameters have been determined for 2g q12h and 4g/24h (De Jongh et al., JAC 2008): 4g seems sufficient on average but might be not enough for some patients with large Vd

- Since Vd can be highly variable in critically ill patients, we have explored the possibility to increase the dose up to 6g per day
Aim of the study

- Pharmacokinetics and safety of 6g daily of Temocillin
- Comparison of conventional administration (2g q8h – TID) vs. 6g/24h in continuous infusion (CI)
- PK/PD analysis

Population: Critically ill patients with documented infection due to a Gram negative bacteria susceptible to Temocillin

Setting: 2 Intensive care Units (1 teaching hospital, and 1 general hospital)
### Patients

Total patients randomized: 16

<table>
<thead>
<tr>
<th></th>
<th>TID</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of infection (positive blood cultures)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LRTI</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>IAI</td>
<td>3 (1)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>UTI</td>
<td>1 (1)</td>
<td>1</td>
</tr>
<tr>
<td><strong>age (year ± SD)</strong></td>
<td>64 ± 13</td>
<td>70 ± 11</td>
</tr>
<tr>
<td><strong>SOFA score (SD)</strong></td>
<td>6.5 ± 3.0</td>
<td>8.4 ± 3.8</td>
</tr>
<tr>
<td>creatinine clearance (ml/min ± SD)</td>
<td>83 ± 33</td>
<td>51 ± 28</td>
</tr>
<tr>
<td><strong>Treatment duration (days ± SD)</strong></td>
<td>4.6 ± 1.5</td>
<td>5.2 ± 2.1</td>
</tr>
</tbody>
</table>
Conventional administration

![Graph showing concentration TMO (mg/L) over time (h)].

- **TOTAL** line starts high and decreases rapidly, then stays nearly flat for several hours, before rising sharply towards the end.
- **FREE** line starts lower than the TOTAL line, shows a slight decrease, and then remains relatively flat before increasing towards the end.

Key points:
- Time (h) range: 0 to 49
- Concentration TMO (mg/L) range: 0 to 225

32, 16, 8 markers indicate specific concentration levels at certain times.
Continuous infusion

![Graph showing concentration of TMO over time](image)

The graph illustrates the concentration of TMO (mg/L) over time (h) for both TOTAL and FREE forms. The concentration decreases over time, with TOTAL showing a gradual decline and FREE remaining relatively constant. At specific time points, the concentration values are marked: 32 (TOTAL), 16 (FREE), and 8 (TOTAL).
<table>
<thead>
<tr>
<th>PK/PD parameters</th>
<th>TID</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean % of the time where the free fraction remains above (Monte Carlo simulation for 2g q8h, De Jongh et al. JAC 2008)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 mg/L (100%)</td>
<td>100 %</td>
<td>100 %</td>
</tr>
<tr>
<td>16 mg/L (80%)</td>
<td>83 %</td>
<td>100 %</td>
</tr>
<tr>
<td>32 mg/L (27%)</td>
<td>20 %</td>
<td>57 %</td>
</tr>
<tr>
<td>Mean lowest free concentration ± SEM (mg/L)</td>
<td>14 ± 3</td>
<td>29 ± 7</td>
</tr>
</tbody>
</table>

Mean ascite concentration: 28 mg/L (range 14 – 45 mg/L)
Concentration ratio between free serum concentration and free ascite concentration: 90% [range: 42 -166%]
## Outcomes

<table>
<thead>
<tr>
<th></th>
<th>TID (8)</th>
<th>CI (8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cured / discharged</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>TMO not indicated</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>(retrospective)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death *</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Safety outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events related to temocillin</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* patient under TID died of septic shock due to coagulase negative Staphylococcus during treatment; patient under CI died after cure of the Gram negative infection of septic shock due to *E. facium* and *B. fragilis*
Conclusions

- TMO is safe at the posology of 6g per day
- If TID seems sufficient to achieve PK/PD goal for beta-lactam efficacy, CI allow a better efficacy margin considering the breakpoint (16 mg/L)
- These data suggests that the optimal dose for TMO in critically ill without renal replacement therapy should be increased to 6g daily