Assessment of dosage regimens of tigecycline in hospitalised patients

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Introduction
Tigecycline is the first available glycycycline derived from minocycline. It possesses broad-spectrum activity against aerobic and anaerobic bacteria including multidrug resistant gram positive and gram negative pathogens. No data regarding Therapeutic Drug Monitoring (TDM) application to tigecycline administration are available.

Objectives
Study of various dose regimens for the antibiotic tigecycline in a group of 14 hospitalized patients and assessment of the potential applicability of TDM for this drug.

Methods
Blood samples from 14 hospitalised patients were collected, during treatment with tigecycline. The patients were treated for about 2 weeks and were administered either 50 mg bid (8 patients) or 50 mg tid (6 patients) with or without a loading dose of 100 mg. The quantification of tigecycline in patients plasma was conducted with an HPLC method. Minocycline was used as internal standard in the sample preparation in order to minimize the impact of potential variances in experimental conditions. The mobile phase consisted of 0.070M phosphate buffer with pH 7.1 and acetonitrile, appropriate for detections in the far UV, with volume ratio 76:24 (v/v). The detection length that was used is 350 nm, the flow rate was 1ml/min and the injection volume 50 μL.

Tigecycline assay [1]:

Calibration Curve

- 25 μl. of a stock solution (100 μg/ml) to make a range of C (μg/ml) from 1.0 μg/ml
- 25 μl. of a stock solution (50 μg/ml) to make a range of C (μg/ml) from 0.2 μg/ml

Samples

- 500 μl plasma
- Vortex for 1-2 min
- Centrifugation (4000 rpm, 5°C, 15 min)
- Vortex for 1-2 min
- Centrifugation (4000 rpm, 5°C, 15 min)
- Injection of 50 μl of the clear supernatant

Modeling and Simulations
We used literature population priors for two-compartment pharmacokinetic parameters [2] (see table 1), and the following covariate model for clearance [2]:

\[ CL = 19.6 + (10.2 \times (BSA - 1.73)) + 0.0638 \times (CrCl - 100) \]  

Table 1. Parameter values taken from literature and used for the EBE estimates and the MC simulations.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean</th>
<th>BSV %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/hr)</td>
<td>Eq. 1</td>
<td>40.4</td>
</tr>
<tr>
<td>V1 (L)</td>
<td>65.2</td>
<td>82.1</td>
</tr>
<tr>
<td>Q (L/hr)</td>
<td>85.1</td>
<td>110</td>
</tr>
<tr>
<td>V2 (L)</td>
<td>398</td>
<td>40.2</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.83</td>
<td>12.6</td>
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<tr>
<td>CrCl (ml/min/1.73 m²)</td>
<td>79.7</td>
<td>44.0</td>
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</tbody>
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Conclusions
• A significant number of patients (25%) were found to be subtherapeutic risk for the 2x50 mg dose while no patients were found subtherapeutic for the 3x50 mg dose.
• However, adverse events were observed to a significant number of patients (60%) for the 3x50 mg dose.
• Therefore TDM may be applicable to tigecycline treatment.

References
1. Zorbas K, Valsami G, Vryonis E, Skoutelas A, Archontaki H. Robust and Sensitive Liquid Chromatographic/UV detection technique for the determination of tigecycline in rabbit plasma, J AOAC Int. 2011; accepted for publication.