A minimal physiologically-based pharmacokinetic model to investigate CNS distribution of metronidazole in ICU patients

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Introduction

- Metronidazole is used to treat brain infections due to anaerobic bacteria. A better understanding of anti-infective drugs pharmacokinetics (PK) in the CNS is clearly needed [1, 2].

- Minimal Physiologically-Based Pharmacokinetic (PBPK) modelling approach is valuable to describe drug disposition from a mechanistic standpoint [3]. The alternative minimal PBPK models inherit major physiological attributes of whole-body PBPK models and offer a more rational basis than compartmental models [3].

- Objective: To develop a minimal PBPK model in order to characterize metronidazole PK in plasma, brain extracellular fluid (ECF) and ventricular cerebrospinal fluid (CSF) in ICU patients.

Material & Methods

1. Study design

- Height male patients (median age: 56±12 years, weight = 87±13 kg) were included in the analysis. They received a 30-min IV infusion of 500 mg metronidazole every 8 h.

- CSF samples were collected in 4 patients with high intracranial pressure (ICP) via an external ventricular drainage (EVD) system into the lateral brain ventricles. CSF samples were collected at one occasion at steady state.

- ECF concentrations were measured in 4 other patients with traumatic brain injury by microdialysis technique at one occasion at steady state [2].

- Blood samples were collected simultaneously. Plasma unbound fraction was determined by ultrafiltration and all samples were assayed by LC-MS/MS [2].

2. Minimal PBPK model

- The CNS was represented by 3 compartments: the brain vasculature, the brain ECF and the brain CSF. The rest of the tissues were lumped as a single, perfusion limited and well-stirred tissue compartment (Figure 1).

- The tissue compartments were connected via blood flow (Q) to a plasma pool in a closed-loop format.

- Volumes (V) and blood flows were fixed to their physiological value obtained from literature [4-8].

- Metronidazole elimination was implemented as a total unbound plasma clearance representing both its renal excretion and hepatic metabolism [4].

- Dialysates, collected as fractions during various time intervals, were modeled as the integral over each collection interval [9].

- The model well described unbound metronidazole PK profiles in plasma, ECF and CSF (Figures 2-3).

- No active transport was implemented in the model but the bidirectional passive diffusion across the BBB was estimated to be almost 10 times more rapid (PS\textsubscript{ECF} = 1.56 L/h) than across the BCSFB (PS\textsubscript{CSF} = 0.176 L/h) (Table 1).

Table 1. Typical estimates for metronidazole pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical value</th>
<th>IV CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>K\textsubscript{in}\textsubscript{ECF}</td>
<td>0.799 (7.4)</td>
<td></td>
</tr>
<tr>
<td>CL\textsubscript{ECF} (L/h)</td>
<td>7.28 (10.9)</td>
<td>33.6 (47.6)</td>
</tr>
<tr>
<td>PS\textsubscript{ECF} (L/h)</td>
<td>1.56 (42.1)</td>
<td>-</td>
</tr>
<tr>
<td>PS\textsubscript{CSF} (L/h)</td>
<td>0.176 (65.2)</td>
<td>-</td>
</tr>
</tbody>
</table>

3. Results

- The elimination of metronidazole from the CSF compartment was implemented using EVD flows (Q\textsubscript{EVD}), determined experimentally, as a covariate.

- As EVD is set when the outflow of CSF (Q\textsubscript{CSF-out}) is obstructed, Q\textsubscript{CSF-out} = physiological Q\textsubscript{CSF-out} - Q\textsubscript{EVD} in this case.

- Parameters values were estimated using NONMEM 7.4.

Conclusion & Perspectives

- Metronidazole demonstrated an extensive distribution through BBB and BCSFB, governed by passive diffusion. These results are consistent with the fact that metronidazole is not known to be a substrate of efflux transport systems at the CNS level.

- The distribution clearance across the BBB (PS\textsubscript{ECF}) was more rapid than the distribution clearance across the BCSFB (PS\textsubscript{CSF}), consistent with the larger surface area of BBB relative to the BCSFB [10].

- The minimal PBPK model will then be used to make simulations in various dosing regimen or/and physiological situations.

References

[1] Nau et al., Clin Microbiol Rev. 2010