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].

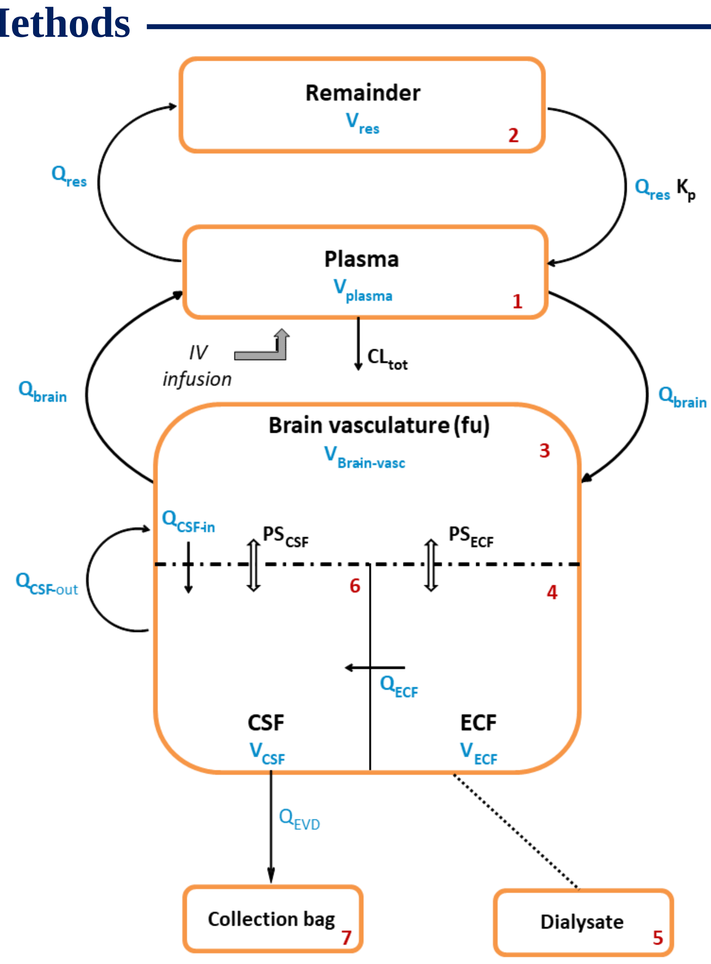

Figure 1. Schematic representation of metronidazole minimal PBPK model: parameters in blue are set to their physiological value or fixed and parameters in black are estimated. The dashed line represents the blood-brain barrier (BBB) and the blood-CSF barrier (BCSFB), PS the clearance distribution across both the BBB and the BCSFB.

- The elimination of metronidazole from the CSF compartment was implemented using EVD flows (Q_{EVD}), determined experimentally, as a covariate.
- As EVD is set when the outflow of CSF ($Q_{CSF-out}$) is obstructed, $Q_{CSF-out} = physiological\ Q_{CSF-out} - Q_{EVD}$ in this case.
- Parameters values were estimated using NONMEM 7.4

Results

- 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_{ECF} = 1.56 L/h) than across the BCSFB (PS_{CSF} = 0.176 L/h) (Table 1).

Table 1. Typical estimates for metronidazole pharmacokinetic parameters

Parameter	Typical value (RSE%)	IIV CV% (RSE %)
Kp_{res}	0.799 (7.4)	-
CL_{tot} (L/h)	7.28 (10.9)	33.6 (47.6)
PS_{ECF} (L/h)	1.56 (42.1)	-
PS_{CSF} (L/h)	0.176 (65.2)	-

RSE: Relative Standard Error ; IIV: Inter-individual Variability ; CV = Coefficient of Variation

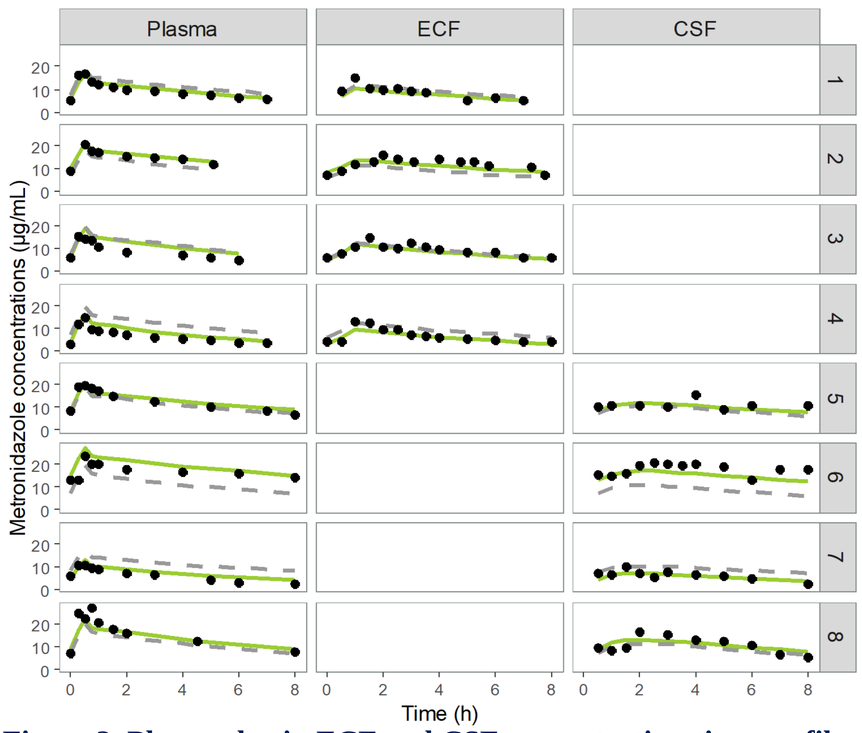

Figure 2. Plasma, brain ECF and CSF concentration-time profiles for metronidazole. The circles represent the observed data, the green solid lines the individual predictions and the grey dashed lines the population predictions.

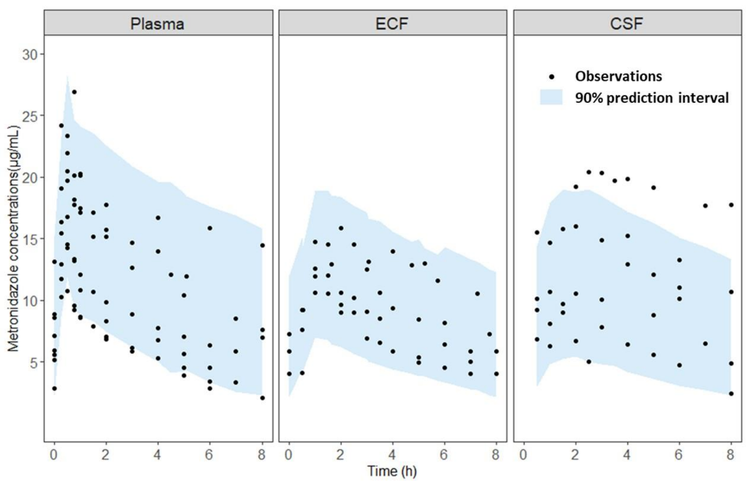

Figure 3: Visual predictive checks of the final PBPK model for unbound metronidazole plasma, ECF and CSF concentrations. Circles represent observed data and the blue-shaded area depicts the 90% prediction interval for 1000 simulated profiles.

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_{ECF}) was more rapid than the distribution clearance across the BCSFB (PS_{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 physio-pathological situations.

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