Prediction of serum and cerebrospinal fluid concentrations of carbamazepine: An application of parameter estimation and the permeability limited 4-compartment brain model in Simcyp®

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Objective:

To predict the concentration of carbamazepine (CBZ) in cerebrospinal fluid (CSF) of humans using the permeability limited 4-compartment brain model in Simcyp® V11 and the default library values for populations related values.

Methods:

A total of 108 steady state serum CBZ, carbamazepine-10, 11- epoxide (CBE) and 12 single point pre-dose CSF concentrations from 14 male individuals (age 14 – 44 years, dose range 600-2000mg daily in 2-4 divided doses) were extracted from literature [1].

Step 1 - a Top-Down approach: The expectation maximisation algorithm within the Simcyp parameter estimation (PE) module was used to optimise the CBZ and CBE parameters using dose normalised concentrations of CBZ and CBE. All the parameters were assumed to be log-normally distributed. Model selection was based on objective function values and goodness of fit plots.

Step 2 - a combination of the Top-Down and Bottom-Up approaches: The retrograde model was used for parent drug to calculate intrinsic clearance values from oral clearance (CLpo) for CBZ metabolism by CYPs 3A4, 3A5 and 2C8, the CLpo for the metabolite was used directly as an *in vivo* input into the Simcyp Simulator.

Step 3 - a Bottom-up approach: The final model was used to predict the concentration of CBZ in CSF using the permeability limited 4-compartment brain model in Simcyp (Figure 1) assuming passive diffusion of CBZ into brain. The permeability surface area product of BBB (PSB) and permeability surface area product of BCSFB (PSC) parameters in the brain model (see Figure 1) were assumed to be 2.1 and 0.0021 L/h respectively.

The simulated CSF concentrations were compared with the observed values.

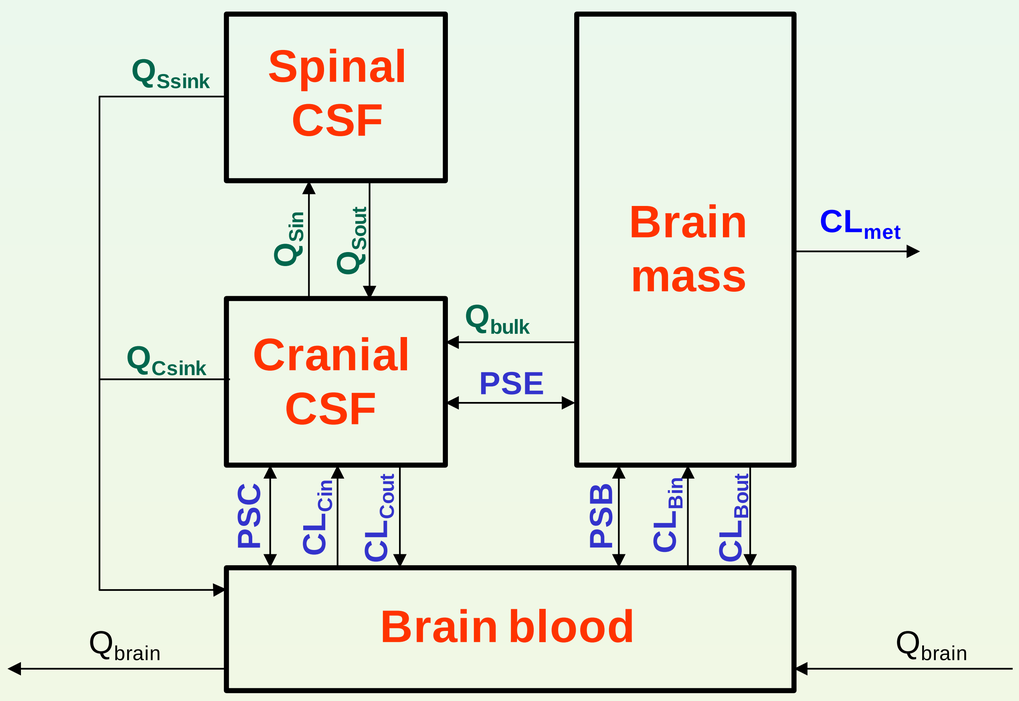

Figure 1: Schematic representation of the permeability-limited 4-compartmental brain model

Results:

A full PBPK model with first order absorption provided the best fit to the CBZ serum data. The metabolite data was well described by a minimal PBPK model (Results not shown). A combined error model was the best residual error model for both parent and metabolite. The estimated CLpo and ka of carbamazepine was (mean (CV%)) 6.39 (36) L/h and 0.09 (6) h^{-1} respectively. The estimated CLpo for the metabolite was 0.09 (12) L/h. The calculated intrinsic clearance values from oral clearance (CLpo) for CBZ metabolism by CYPs 3A4, 3A5 and 2C8 were 0.03, 0.001 and 0.0003 L/h. Visual predictive checks (VPC) for CBZ in serum is shown in Figure 2. The observed 5th and 95th percentile of the predicted CSF concentrations for CBZ are shown in Figure 3.

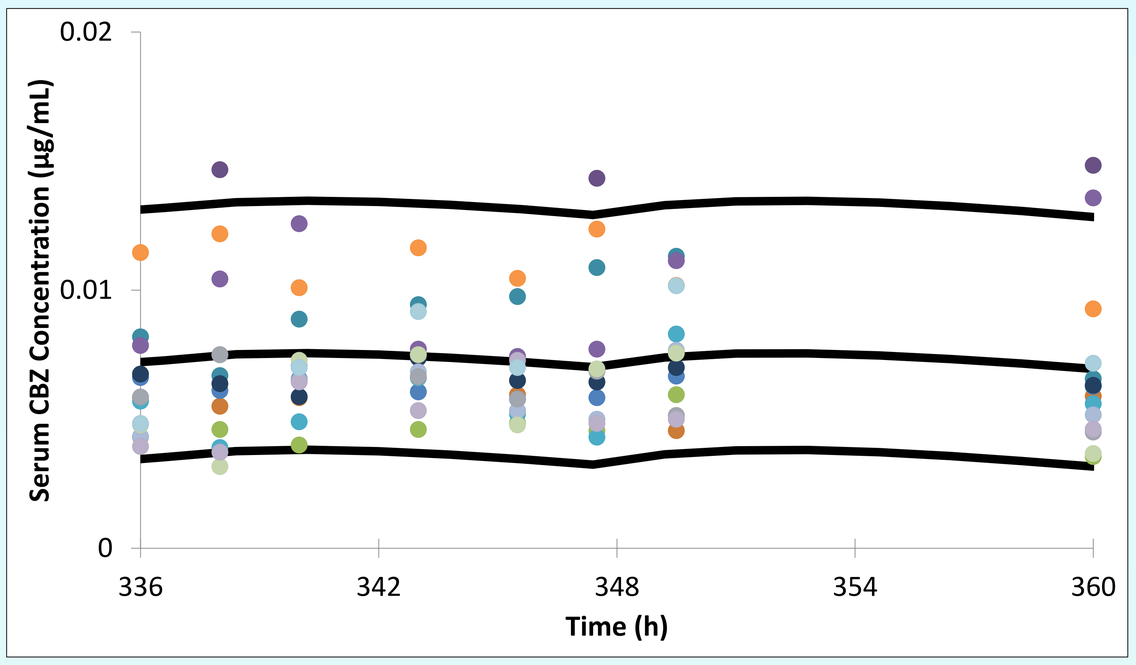

Figure 2: VPC showing the observed individual CBZ concentrations at steady state in serum (·) median, 5th and 95th percentile of model predictions (-).

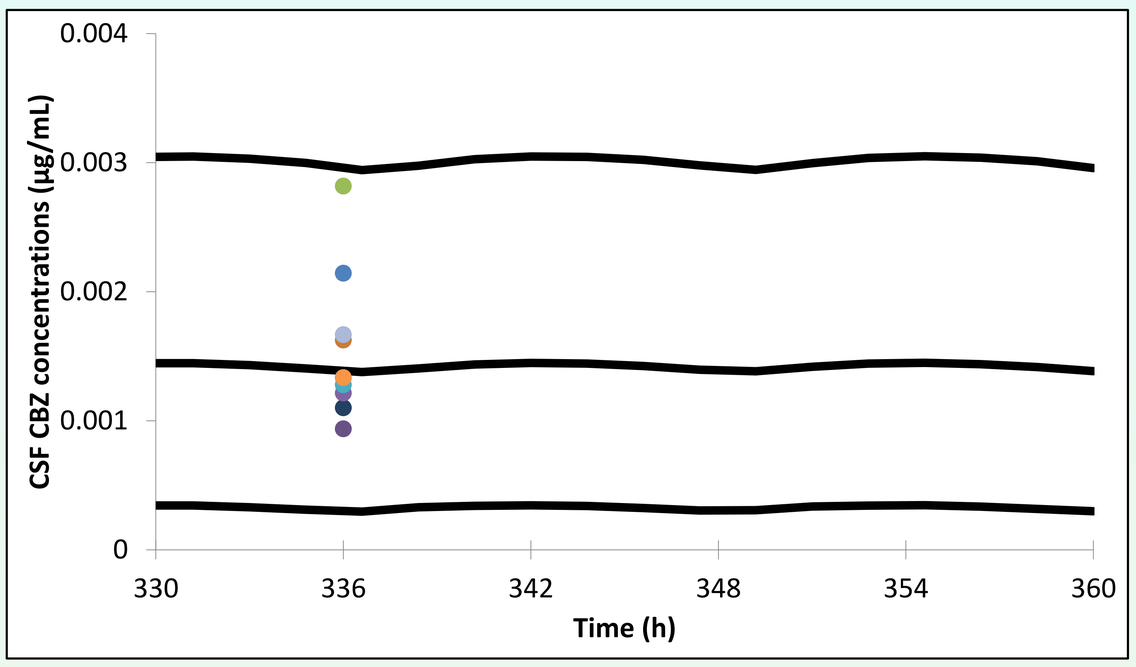

Figure 3: VPC showing the observed individual CBZ concentrations at steady state in CSF (·) median, 5th and 95th percentile of model predictions(-)

Discussion:

The full PBPK model predicts the concentration of CBZ in serum using a combination of Top-Down and Bottom-Up approaches. The observed CSF concentrations of CBZ (from literature) fell within the 95th percentile interval of the model predictions, all predicted values were within 2.1-fold of observed values. Transporters in the brain may not play a role in the transfer of CBZ from plasma to brain, which is in agreement with published literature [2].

Conclusion:

The model successfully predicted the concentration of CBZ in CSF using this three stage modelling that combined the Top-Down and Bottom-Up approaches in various stages. An application of the permeability-limited 4-compartment brain model in Simcyp was demonstrated.

References:

1. Johannessen SI *et al.,* Br. J. Clin. Pharmacol., 1976,3,575-582
2. Owen A *et al.,* Br. J. Clin. Pharmacol., 2001,51,345-349