PHYSIOLOGICALLY-BASED PHARMACOKINETICS (PBPK) WITH AND WITHOUT DIFFUSION LIMITED PERMEABILITY: MODELLING DRUG CONCENTRATION-TIME PROFILE IN BRAIN

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Objective 1

To provide, through modeling, an example of potential disparity in drug concentration-time profile in brain between paediatric and adult populations. Known physiological parameters were used where the drug assumed to penetrate the brain passively. The necessary dose adjustment was made to keep drug plasma concentration the same for both groups.

Description of the PBPK model

A whole-body PBPK model consisting of 13 perfusion-limited compartments representing various tissues and organs (Figure 1), as implemented within the Simcyp Population-based Simulator (Jamei *et al.*, 2009), was used for simulating the brain concentration considering the physiological and anatomical changes in paediatric and adult groups.

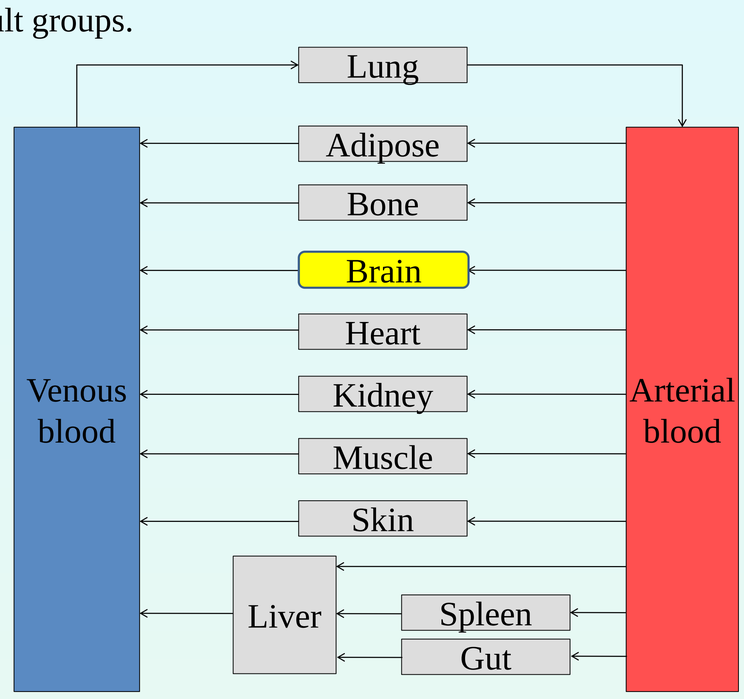


Figure 1. PBPK model with perfusion-limited brain compartment

The model was used to evaluate oral and iv administration of 4 compounds with varying tissue-to-blood ratios (Kp), namely diclofenac (Dicl.), theophylline (Theo.), sildenafil (Sild.) and dextromethorphan (Dextr.). The ratios of the maximum drug concentration in brain and plasma (Cmax,br/Cmax,pl) in paediatrics were compared with those in adults.

Simulation outcome

Major disparities in Cmax ratios were observed, particularly for the compounds with high Kp values (Sild. and Dextr.) between paediatrics and adults (Figure 2). The discrepancies were related to age, route of administration, and the drug properties.

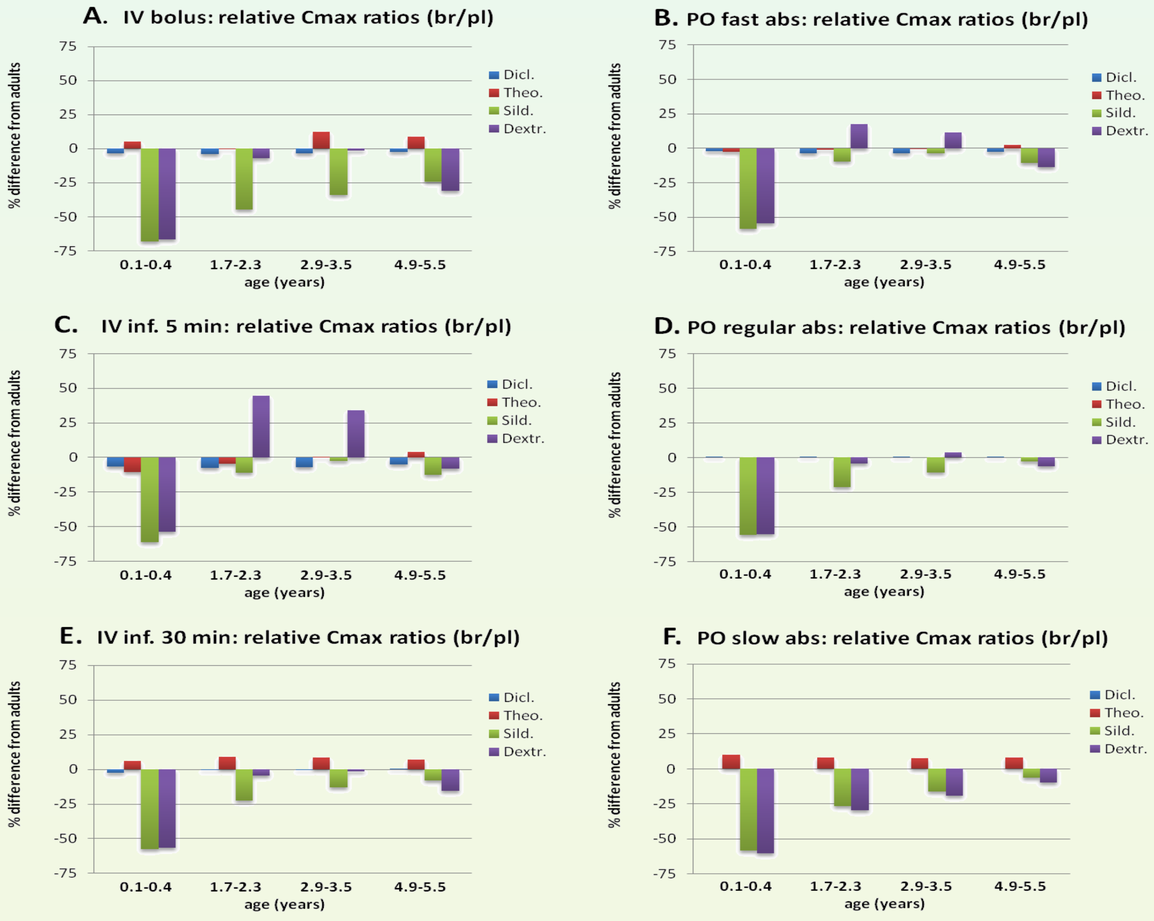


Figure 2. Disparity of Cmax ratio in paediatrics *vs*. adults with oral (A, C, E) and iv (B, D, F) doses

Remark 1

The discrepancies observed in the "absence of any transporter" related effects in the blood-brain barrier (BBB) are simply due to physiological changes occurring during the first few years of life particularly those related to brain blood perfusion.

Objective 2

To expand the lumped brain model in the previous PBPK and consider modeling of the transporter effects on drug disposition in the brain.

Active transport in brain barriers

Drug disposition into the brain and cerebrospinal fluid (CSF) is primarily limited by three barriers, namely the BBB, the blood-CSF barrier (BCSFB) and the ependyma (CSF-brain barrier) (Figure 3). Literature were reviewed to collate brain physiological and anatomical attributes as well as any information on transporter abundance and activities on the BBB and BCSFB.

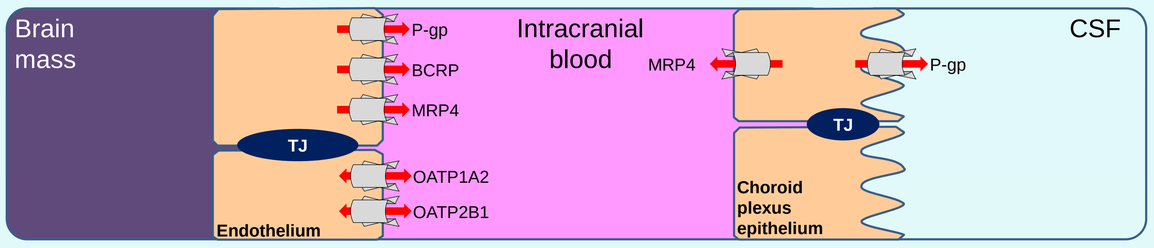


Figure 3. Major transporters on BBB and BCSFB

Diffusion-limited brain model

The information on physiological and anatomical attributes were relatively abundant however there was a major shortcoming regarding the level of transporters and their activities (Table 1). A 4-compartment diffusion-limited brain model was developed and implemented in Matlab Simulink®. The model divides CSF into 2 compartments namely cranial and spinal sections (see Figure 4).

Table 1. Parameters availability in brain model

Parameter	Intracranial blood	Brain mass	Cranial CSF	Spinal CSF
Volume	☑	☑	☑	☑
Flow rate	☑	☑	☑	☑
pH	☑	☑	☑	☑
Protein	☑		☑	☑
Enzyme	☑		☑	☑

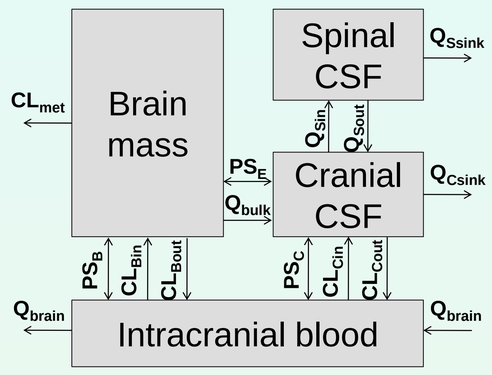
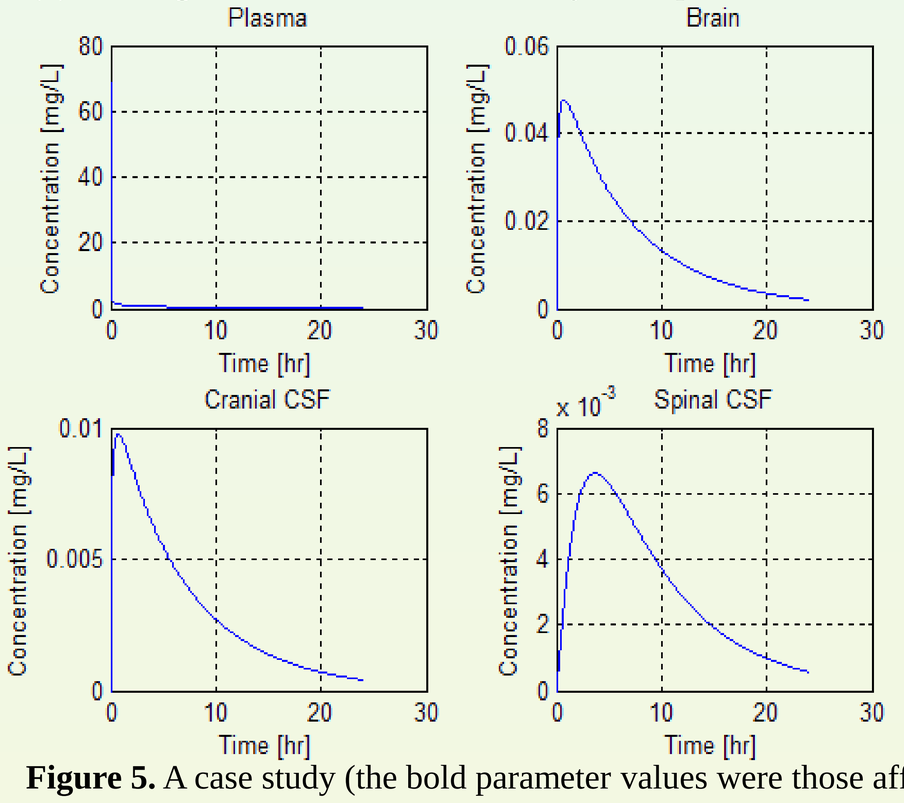


Figure 4. Structure of 4-compartmental diffusion-limited brain model

Simulation outcome

The model facilitated exploring the drug distribution into brain and CSF after combining it with whole-body PBPK model. Various scenarios were investigated to explore the effects of transporters on drug disposition in brain and CSF. Preliminary simulation results (e.g. Figure 5) have shown that, (1) depending on the drug properties the concentrations in the spinal CSF might be very different from that of the cranial CSF; (2) the latter may or may not reflect the drug concentrations in brain mass; and (3) the drug concentrations in blood may not represent those in brain mass.



Compound: Quinidine
Dose: iv 200 mg

Assumed parameters:
PS_B=2.1 mL/hr;
PS_C=2.1 µL/hr;
PS_E=300.0 L/hr;
CL_{Bin}=0.0;
CL_{Bout}=5.25 L/hr;
CL_{Cin}=0.21 L/hr;
CL_{Cout}=0.042 L/hr;
CL_{met}=0.

Figure 5. A case study (the bold parameter values were those affected by transporters)

Remark 2

Consistent with reported clinical studies, the model was able to show the disparities in drug concentration-time profiles in blood (or plasma), brain mass, cranial and spinal CSF which was related to drug properties, particularly transporter affinities.

Conclusions and further development

- The age-dependency of drug disposition in brain can be due to physiological growth and not the effect of transporter expression on brain barriers.
- Development of a diffusion-limited brain model allows incorporation of transporters as well as physiological and pathological changes in the CNS drug disposition.
- On the basis of observations, the 4-compartmental diffusion-limited brain model is now being incorporated within the Simcyp Population-based Simulator.

***Reference*:** Jamei *et al. DMPK*, 2009.

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