Development of a pediatric brain PBPK model in children with and without meningitis.

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Currently, several pediatric PBPK models have been developed incorporating developmental changes affecting plasma drug disposition. Disposition into cerebrospinal fluid(CSF) is also age-related and affected by, among others, CSF production rate. In addition, drug disposition can be affected by brain diseases such as meningitis, which has been described to impair blood-brain barrier integrity. Clinical studies are, however, often not feasible or desired for critically ill children.

Aim
Our aim was to develop a pediatric brain PBPK model to predict CSF concentrations in children with and without meningitis.

Methods
A pediatric PBPK CSF model was developed incorporating age-appropriate parameters and associated inter-individual variability. Literature derived PopPK clearance parameters were used to describe elimination from the model. The CSF model was validated using paracetamol, ibuprofen, flurbiprofen and naproxen. Subsequently, to add the impact of meningitis to the model, meropenem blood-brain barrier penetration was estimated using sensitivity analysis, and validated for the pediatric meningitis population. Plasma and CSF drug observations derived from literature were used to perform visual predictive checks and to calculate ratios between simulated and observed AUCs in order to evaluate model performance.

Results
Simulated data is comparable with observed data both for drugs used to validate the healthy PBPK model, as well as for the meningitis model over a broad age range (age range: 1day – 15years postnatal age). In addition, the ratios between observed and simulated AUCs were within 2-fold difference for all simulations both in plasma and in CSF, indicating acceptable model performance. Disposition of meropenem into the brain was slow. Several days were needed to achieve CSF steady state concentrations whereas in plasma steady state was reached within a day.

Discussion
This pediatric brain PBPK model is an innovative tool to predict CSF concentrations in children with and without meningitis as, next to evaluating pharmacokinetics of mentioned drugs, it can be used as a template model for other drugs acting in the CNS.