Comparison of in vitro and in vivo metabolic clearance estimates for the prediction of caffeine and theophylline pharmacokinetics in adults, children and neonates using a physiologically based model

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INTRODUCTION

• Modelling and simulation is becoming an increasingly important part of the drug development process and may prevent unnecessary clinical studies or allow their more rational design.
• Simcyp provides a platform for modelling and simulation of drug absorption, distribution, metabolism and excretion (ADME) in virtual populations.
• In vitro-in vivo (IVIVE) extrapolation of drug clearance (CL) is combined with a physiologically based pharmacokinetic (PBPK) model, and absorption model to allow PK predictions with associated variability.
• Simcyp Paediatric incorporates additional information on developmental physiology and ontogeny of elimination pathways and has been used successfully to predict drug clearance in neonates, infants and children.
• The latest version of the Paediatric Simulator allows the prediction of concentration-time profiles and has increased options for estimation of metabolic clearance.

OBJECTIVE

• To investigate the ability of two methods of CLint determination: in vitro kinetic data (Vint, Kint) in vivo data using a retrograde model to predict plasma–concentration time profiles of the CYP1A2 substrates caffeine (CAFF) and theophylline (THEO) in neonates, children and adults.

METHODOLOGY

• Physicochemical and in vitro permeability data for CAFF and THEO contained within the Simcyp V9.10 Compound Database were used in all simulations. The PBPK model used was based on that described by Rogers and Rowland2.
• Estimates of in vitro CLint were calculated from literature Vint / Kint data determined using recombinantly expressed CYPs (rhCYP). Vint values were scaled to humanised values using an inter system extrapolation factor (ISEF) and Kint values were corrected for microsomal binding.
• For the retrograde model either i.v. (THEO) or oral (CAFF) data was used to back calculate a CLint value (L/h; Eq 1 and 2). The proportional contribution of each enzyme was calculated for CAFF (CYP1A2 99%, CYP2E1 & CYP3A4 < 1%) and THEO (CYP1A2 = 89%, CYP2D6, CYP2E1 & CYP3A4 =15% each).

• Enzyme specific values of CLint (L/h) were converted to a rate per pmol enzyme using average healthy volunteer population values of CYP abundance (pmol/mg), MPPGL (mg/g) and liver weight (g) (Simcyp Population Database V9.10).
• CLint values were then entered into the Simcyp Simulator V9.10 (adults) and Paediatrics (neonates and children).
• Simulations replicating a range of adult and paediatric in vivo studies were performed for both CLint methods (Table 1).
• Simulated concentration-time profiles were compared against literature profiles both visually and in terms of AUC ratio (Eq 3).
• The AUC ratios for each drug and CLint method were combined to give an overall weighted ratio (Eq 4). Weighting was calculated using Eq 5, where n is the number of subjects in the ith study and N is the total number of subjects in all studies for that age group. The closer the AUC ratio to one the better the AUC estimate.

RESULTS

• Representative concentration–time profiles from In Vitro method for CAFF and THEO in adults and children are shown in Figure 1.
• Overall results for the different CLint methods in the different age groups are summarised in Table 2.
• Despite some under and over prediction of AUC, overall most weighted mean predictions were within 2-fold of observed values. A wide overlap in the range of AUC values predicted using the two CLint methods was observed.

METHOD B: CLint from Retrograde Model

$$CL_{int} = \frac{Q_{h} \times CL_{ret}}{f_{u} \times (Q_{h} - CL_{int})} \quad (Eq \ 1)$$

$$CL_{int} = \frac{CL_{ret} \times F_{u} \times F_{o}}{f_{u}} \quad (Eq \ 2)$$

Where CLret is the hepatic blood CL (CLint-CLu), Qh is hepatic blood flow, fu is fraction unbound in blood, CLu is oral clearance, Fo is fraction escaping gut metabolism and fu is fraction absorbed.

CONCLUSIONS

• Overall the predicted concentration-time profiles for CAFF and THEO were close to the in vivo studies for adults and children.
• For CAFF the under-prediction of AUC in neonates is due to many of the studies involving premature babies. At present there is a lack of information on prematurity in the Simcyp Paediatric model.
• There was little difference in performance between the CLint methods in terms of predicting the PK of CAFF and THEO from birth onwards. This suggests that the in vitro metabolic input values used are accurate for CAFF and THEO.
• Full evaluation of the different CLint input methods requires extension of the current analysis to incorporate a range of drugs metabolised by different CYP enzymes.

REFERENCES