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[1].
- 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 CL_{int} determination :
  - *in vitro* kinetic data (V_{max}, K_m)
  - *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 Rowland[2].
- Estimates of *in vitro* CL_{int} were calculated from literature V_{max} / K_m data determined using recombinantly expressed CYPs (rhCYP). V_{max} values were scaled to humanised values using an inter system extrapolation factor (ISEF) and K_m values were corrected for microsomal binding.
- For the retrograde model either *i.v.* (THEO) or oral (CAFF) data was used to back calculate a CL_{int} value (L/h; Eq 1 and 2). The proportional contribution of each enzyme was calculated for CAFF (CYP1A2 99%, CYP2E1 &CYP3A4 < 1% each) and THEO (CYP1A2 =89 %, CYP2D6, CYP2E1 & CYP3A4 <1% each)

METHOD B: CL_{int} from Retrograde Model

$$CL_{\text{int}H} = \frac{Q_H \times CL_{metH}}{fu_B \times (Q_H - CL_{metH})} \text{ (Eq 1)} \qquad CL_{\text{int}H} = \frac{CL_{po} \times F_G \times F_a}{fu_B} \text{ (Eq 2)}$$

Where CL_{metH} is the hepatic blood CL (CL_{iv}-CL_{renal}), Q_H is hepatic blood flow, fu_B is fraction unbound in blood, CL_{po} is oral clearance, F_G is fraction escaping gut metabolism and F_a is fraction absorbed.

- Enzyme specific values of CL_{int} (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).
- CL_{int} 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 CL_{int} 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 CL_{int} method were combined to give an overall weighted ratio (Eq 4). Weighting was calculated using Eq 5, where n_i 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.

$$Ratio = \frac{AUC_{\text{Predicted}}}{AUC_{Observed}} \text{ (Eq 3)} \qquad \text{Weighted Ratio} = \sum_{1}^{n} \left(\frac{AUC_{predicted_i}}{AUC_{observed_i}} * Weight_i \right) \text{ (Eq 4)}$$

$$weight_i = \frac{n_i}{N} \text{ (Eq 5)}$$

Table 1: Summary of caffeine and theophylline *in vivo* studies

Drug	Studies	N	Age (y)	Dose	Route
CAFF-Adult	4 - 8	209	18 - 78	50 – 300 mg	Oral and IV
CAFF-Paediatric	9	5	7 - 10	100 mg	Oral
CAFF- Neonate	10 – 13	99	0.002 – 0.87	5 – 30 mg/kg	IV and Oral
THEO-Adult	14 – 20	67	18 - 50	85 – 257 mg	Oral and IV
THEO-Paediatric	21 - 23	44	1 - 16	3.5 – 5 mg/kg	IV and Oral

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 CL_{int} 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 CL_{int} methods was observed.

Table 2: *Caffeine and theophylline AUC ratios in adults, children and neonates. Values represent weighted AUC plus the range from individual studies*

Drug	CLint Method	Age Groups		
		Adult	Child	Neonates
CAFF	*In vitro* CL_{int}	1.14 (0.02- 1.54)	1.14	0.43 (0.02- 2.65)
	In vivo CL_{int}	1.41 (0.02- 1.71)	1.41	0.47 (0.02- 2.97)
THEO	*In vitro* CL_{int}	0.66 (0.40- 1.11)	0.80 (0.61- 1.15)	-
	In vivo CL_{int}	1.16 (0.81- 1.65)	1.12 (0.84- 1.53)	-

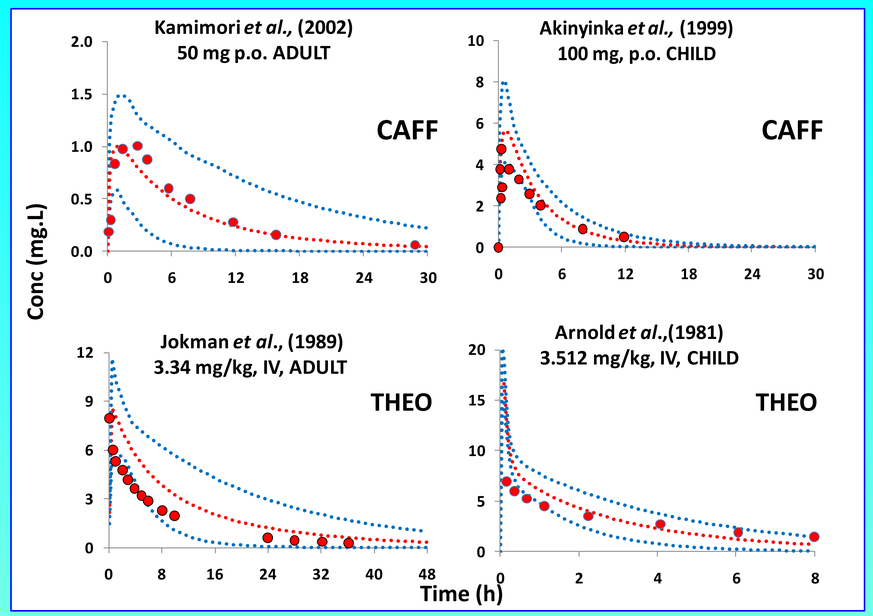

Figure 1: Predicted (using *In Vitro* method) and observed caffeine plasma concentration–time profiles in adults and children for Caffeine and Theophylline. Profiles are from the

In vivo data — Simulated data using *In Vitro* method — 5^{th} & 95^{th} confidence intervals for the simulated data

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 CL_{int} 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 CL_{int} input methods requires extension of the current analysis to incorporate a range of drugs metabolised by different CYP enzymes.

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