Prediction of Drug-Drug Interaction between Phenobarbital and Theophylline in Children using Physiologically-Based Pharmacokinetic Modelling

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Background

Theophylline, despite its narrow therapeutic range, is commonly used in the treatment of reversible airway obstruction and asthma. In clinical practice particular caution is required when prescribing concomitant treatment with this drug. Children with asthma and seizure conditions, may receive both theophylline and phenobarbital [1]. Clinical studies have demonstrated phenobarbital can induce the metabolism of theophylline in adults and children. Physiologically based pharmacokinetic (PBPK) models have been widely used to support submissions to regulatory agencies, and the majority of these cases were related to the prediction of DDI liability. The aim of this study is to evaluate the accuracy of utilising the PBPK models to predict the interaction between theophylline and phenobarbital in children.

Methods

All the simulations were conducted using Simcyp Simulator V18R1. The PBPK models for theophylline and phenobarbital were adopted from Simcyp compound library. The phenobarbital model was further expanded to incorporate *in vitro* derived CYP1A2 induction parameter [2]. The prediction accuracy was evaluated by comparing the simulated plasma concentration-time profiles and PK parameters with observed clinical results in adults and children.

Results

The CYP1A2-mediated metabolism represents 85% of the elimination of theophylline, which was verified by the DDI studies with CYP1A2 inhibitors, ciprofloxacin and fluvoxamine, in adults (Figure 1). Phenobarbital has been developed as a inducer of CYP3A4 and CYP2C9 within Simcyp. *In vitro* studies with human hepatocytes indicated a 1.7-fold induction in CYP1A2 mRNA level after treatment of phenobarbital [2]. This induction parameter was then incorporated into phenobarbital model to simulate the interactions with theophylline. The PBPK models were able to recover the plasma concentration-time profiles of theophylline with or without the presence of phenobarbital in adults and children with (Figure 2 & 3). The predicted change of clearance of theophylline after the co-administration of phenobarbital were within 0.8- to 1.25-fold range of the observed data in adults and children (Table 1).

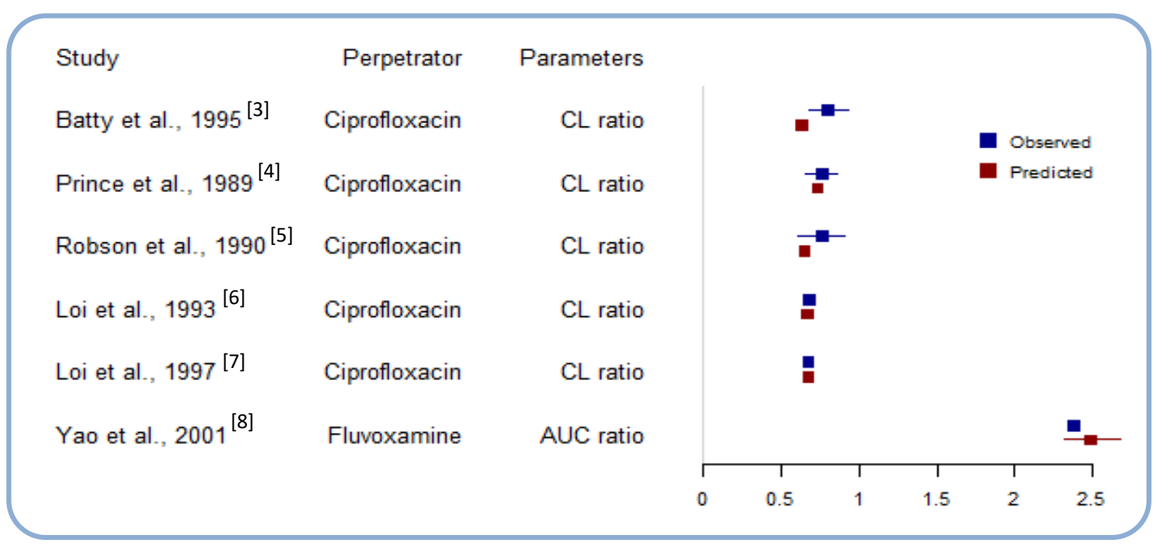

Figure 1. *Predicted vs observed interactions between theophylline and CYP1A2 inhibitors, ciprofloxacin and fluvoxamine.*

Results

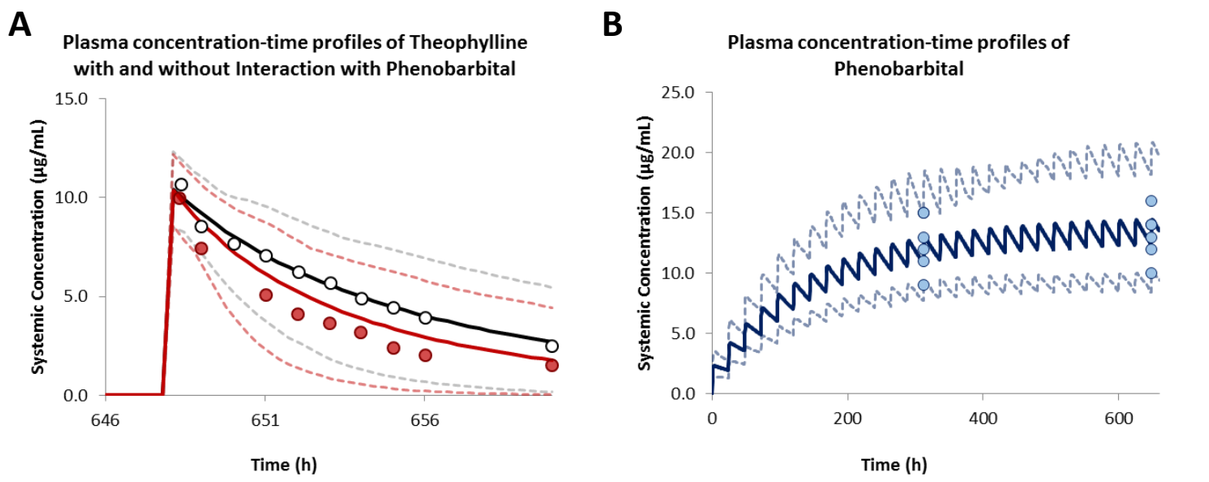

Figure 2. *Simulated (solid lines) and observed (data points [9]) mean plasma concentration-time profiles of (**A**) theophylline after an iv infusion of 3.2 mg/kg over 5 min on Day 28 in the absence (black lines and white points) or presence (red lines and red points) of (**B**) phenobarbital (blue lines and blue points) 90 mg every 24 hours for 28 days. The dashed lines represent the 5th to 95th percentile of the total virtual population (Sim-Healthy Volunteers, 20 trials x 6 subjects, 23- 32 years, 33% female).*

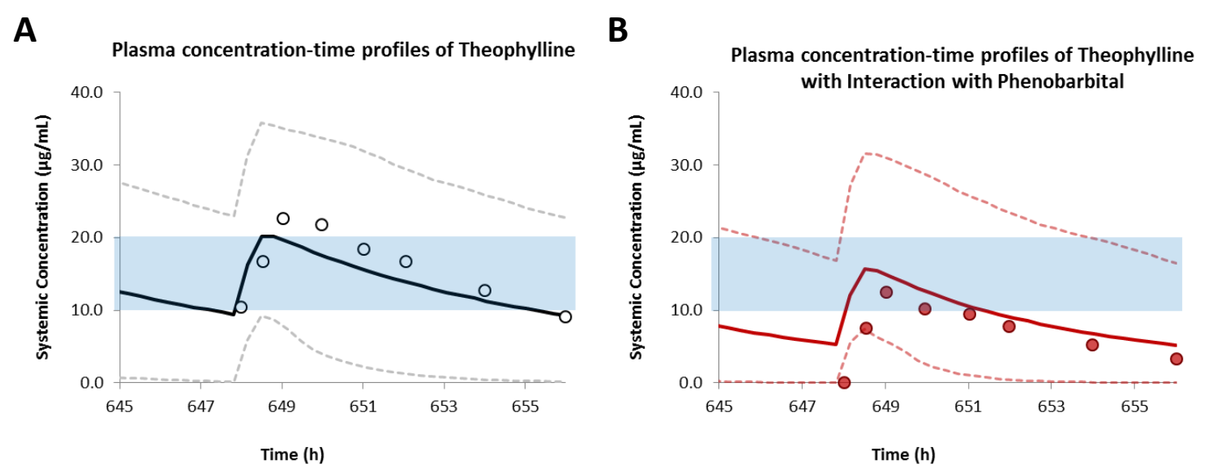

Figure 3. *Simulated (solid lines) and observed (data points [1]) mean plasma concentration-time profiles of theophylline after oral doses of 6.62 mg/kg every 8 hours for 19 days in the absence (**A**, black lines and open circles) or presence (**B**, red lines and red points) of phenobarbital 2 mg/kg every 24 hours from Day 9 to 19. The dashed lines represent the 5th to 95th percentile of the total virtual paediatric population (Sim-Paediatric, 20 trials x 7 subjects, 6-12 years, 14% female). The blue shaded areas represent the target concentration between 10 and 20 µg/mL.*

Table 1. Summary of predicted and observed clearance of theophylline with or without the presence of phenobarbital in adults and children.

Adults	**Observed** [9] Mean ± SD	**Predicted** Mean ± SD	**P/O**
CL (L/hr)	3.13 ± 1.03	3.12 ± 1.90	0.99
CL with inducer (L/hr)	4.16 ± 1.37	4.52 ± 3.31	1.08
CL ratio	1.33 ± 0.21	1.45 ± 0.31	1.09
Children	**Observed** [1] Mean ± SD	**Predicted** Mean ± SD	**P/O**
CL (L/hr)	2.24 ± 0.87	2.46 ± 2.36	1.19
CL with inducer (L/hr)	3.35 ± 1.57	3.81 ± 4.52	1.14
CL ratio	1.61 ± 0.99	1.55 ± 0.40	0.96

Conclusions

This present study has showed a comparable prediction of interaction between theophylline and phenobarbital in children, demonstrating that PBPK modelling can provide a valuable aid in theophylline dose adjustment when co-administrated with phenobarbital in order to achieve adequate and tolerated therapeutic concentration in clinic.

References

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