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Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Predict Ondansetron Pharmacokinetics in Children

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Background

▪ Ondansetron is a 5-hydroxytryptamine3 receptor antagonist for the treatment of chemotherapy, radiotherapy and surgery induced nausea and emesis. Ondansetron is extensively metabolized by Cytochrome P450 (CYP)3A4 and CYP1A2 with minor contribution of CYP2D6 and minimal renal elimination.

▪ Applications of PBPK modeling in pediatrics to better understand and incorporation of growth and maturation effects on drug disposition has been actively investigated in both academia and industry. A recent comprehensive study of pediatric PBPK modeling using nine drugs predominantly eliminated through renal clearance suggested that the predictied clearance values are within 1.5-fold of those observed in most of cases including children between 1 month and 2 years old.

Objectives

CYPs are the major drug-metabolizing enzymes and contribute to the elimination of about 75% of marketed prescription drugs. CYP3A4, CYP1A2 and CYP2D6 are particular important CYP isoforms and responsible for over 75% of the CYP mediated metabolic reactions. Despite the promising applications of pediatric PBPK modeling, the systematic evaluation of the predictive performance of CYP metabolized drugs in pediatric patients, especially those less than 2 years old, is still lacking. The objective of this work was to develop a PBPK model to predict ondansetron PK in pediatric patients across all age groups.

Methods

▪ The ondansetron PBPK model were constructed using a population based ADME simulator, Simcyp v14.1 (Sheffield, UK). A full PBPK model was constructed for ondansetron based on physicochemical properties and clinical observations. Steady state volume of distribution (Vss) was predicted with Poulin and Theil method. The fraction metabolized (fm) of CYP3A4 and CYP1A2 of ondansetron was estimated using clinical interaction studies with rifampin. Intrinsic clearance values (CLint) via CYP1A2 and CYP3A4 were calculated as 0.23 and 0.34 µL/min/pmol of isoform using retrograde method.

▪ Following appropriate verification using adult clinical data, pediatric PK was predicted for ondansetron across all age groups using the pediatric module with application of physiological ontogeny. Ontogeny of CYPs captured in Simcyp pediatric module as described by Johnson et al. and Salem et al. was used. Predictive performance using alternative CYP ontogeny profiles reported by Upreti and Wahlstrom were also investiaged in the infant age group.

▪ Sensitivity of the model to the impact of CYP3A7 contribution on ondansetron clearance values following IV bolus administration of single dose 0.1mg/kg ondansetron in infants (1 month to 2 years old) was investigated using CL_{CYP3A7} values ranging from 0.0343 (10 folds lower than CL_{CYP3A4}) to 0.171 µL/min/pmol (50% lower than CL_{CYP3A4}).

▪ Clinical studies used in model development and verification are listed in Table 1.

Results

▪ Developed ondansetron PBPK model reasonably predicted ondansetron clearance in adults and children across all age groups (Figure 1 and 2). All predictions are within 50% of error of observed values (clearance ratios between 0.78 and 1.03). The concentration-time profiles of ondansetron were also reasonably captured in adults and pediatric subjects (Figure 2).

▪ Apply alternative CYP3A4 ontogeny profile reported by Upreti and Wahlstrom did not increase prediction accuracy in infants (clearance ratios 1.33 and 1.39 for two infant studies).

▪ Sensitivity analysis was conducted in infants (1 month to 2 years) using CL_{CYP3A7} ranging from 0.0343 to 0.171 µL/min/pmol. Across the range of values investigated relative minor changes in plasma ondansetron clearance were noted (4.69 to 4.77L/h), suggesting that CYP3A7 only plays minimal role in ondansetron elimination even in infants down to 1 month.

Results (ct'd)

Table 1. Clinical trial information

Age groups	Age range (yrs)	Number of subject	Male/Female numbers	Dose (route)	Regimen	Comments
Adults	18~40	16	16/0	8mg, IV	Single	Healthy volunteers
Adults	21~41	10	2/8	8mg, IV	QD × 5 days	Healthy volunteers
School aged	7~11	11	5/6	4mg, IV	Single	Surgery
Young children	3~7	10	5/5	2mg, IV	Single	Surgery
Infants	0.083~2	24	13/11	0.1mg/kg, IV	Single	Surgery
Infants	0.083~2	26	14/12	0.3mg/kg, IV	Single	Surgery

Figure 1. PBPK modeling performance

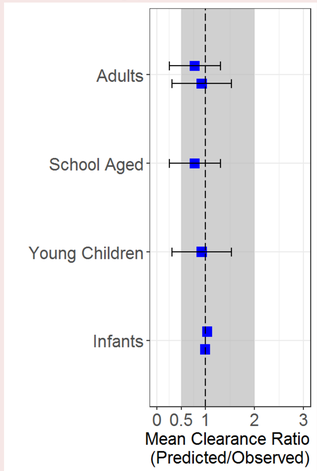
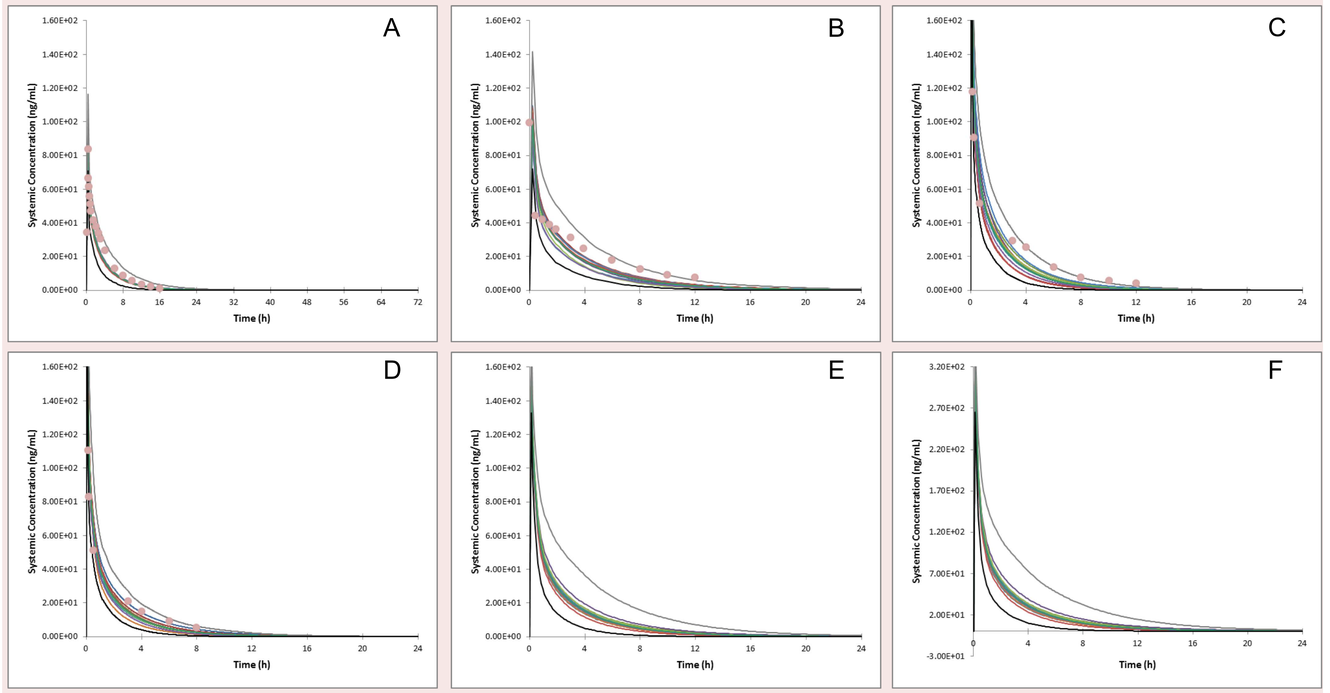


Figure 2. PBPK predicted and clinical observed concentration-time profile of ondansetron



Mean simulated (solid line) and observed (data points) concentrations of ondansetron after IV administration of a single 8 mg dose to healthy adult volunteers (A), 8 mg ondansetron QD to healthy adult volunteers for 5 days (B), single dose 4 mg ondansetron to children 7~11 years old (C), single dose of 2 mg ondansetron to children 3~7 years old (D) and 0.1mg/kg (E) or 0.2 mg/kg (F) ondansetron to infants 1month to 2 years old. The grey lines represent 10 simulated individual trials and the solid black line is the mean of virtual population.

Conclusions

➢ Pediatric PK of ondansetron can be reasonably described using the developed PBPK model by considering ontogeny profiles of CYP3A4 and CYP1A2 built in the Simcyp pediatric model. No predictive performance improvement was observed when predicting ondansetron PK in infants by applying the CYP3A4 ontogeny profiles derived from in-vivo approach.

➢ The contribution of CYP3A7 on overall ondansetron clearance was minimal, even in children between 1 month and 2 years old.

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