PII-154

Predictive Performance of Physiologically Based Pharmacokinetic (PBPK) Modeling of Sufentanil in Children

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Background

- Sufentanil is a potent opioid analgesic widely used as a supplemental or primary analgesic during cardiovascular surgical procedures. Sufentanil is exclusively metabolized by cytochrome P450 (CYP) 3A4 with minimal renal elimination.
- Sufentinal is a CYP3A4 substrate, but its PK was not significantly altered when co-administratered with CYP3A4 inhibitor erythromycin due to its high hepatic extraction rate.
- PBPK modeling has been routinely used to predict drug-drug interaction mediated by CYPs and simulation results have been used to guide dosing in clinical practice. Pediatric PBPK models also show reasonable predictive performance in many drugs metabolized by CYPs

Objectives

CYP3A4 is the major drug-metabolizing enzymes and contribute to the elimination of about 50% of marketed prescription drugs. Despite the promising applications of pediatric PBPK modeling, the predictive performance of drugs metabolized by CYP3A4 with a high hepatic extraction ratio in pediatric patients, especially those less than 2 years old, is rare. The objective of this work was to develop a PBPK model to predict sufentanil PK in pediatric patients across all age groups.

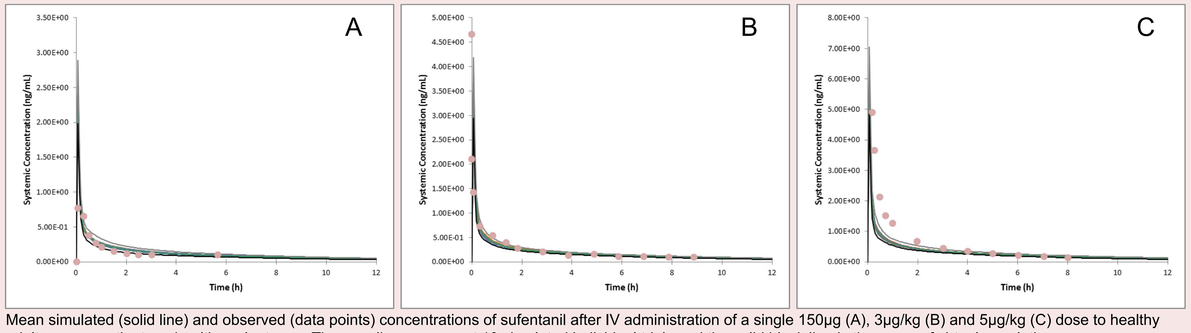
Methods

- The sufentanil PBPK model were constructed using a population based ADME simulator, Simcyp v14.1 (Sheffield, UK). A full PBPK model was constructed for sufentanil based on physicochemical properties and clinical observations. Steady state volume of distribution (Vss) was predicted with Poulin and Theil method.
- The renal clearance of sufentanil was estimated from clinical studies and the fraction metabolized (fm) of CYP3A4 of sufentanil was assumed 100%. Intrinsic clearance values (CLint) *via* CYP3A4 were estimated as 20.74 µL/min/pmol of isoform in adults using retrograde method.
- Following appropriate verification using adult clinical data, pediatric PK was predicted for sufentanil 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.
- Clinical studies used in model development and verification are listed in Table 1.

Results

- Due to the high hepatic extraction ratio, the overall clearance of sufentinal is less determined by CL_{CYP3A4} values and the liver blood flow rate plays a more dominant role in the elimination in adult populations. A sensitivity analysis using CL_{CYP3A4} value ranging between 5 and 100 µL/min/pmol suggested that the impact of CL_{CYP3A4} on overall sufentanil clearance is marginally higher in infants 1 to 10 month old (<1.35 fold) than in adults (<1.15 fold).
- The developed PBPK model reasonably predicted the clearance values of sufentanil in adults and pediatric studies across all age groups. The ratios of mean predicted over observed clearance values are 0.88 (1~10 month), 1.05 (2~23 month), 0.78 (2~9 years), 1.31 (3~11 years), 1.24 (10~15 years) and 1.17 (13~18 years), respectively.

Figure 1. PBPK predicted and clinical observed concentration-time profile of sufentanil in adults



Mean simulated (solid line) and observed (data points) concentrations of sufentanil after IV administration of a single 150µg (A), 3µg/kg (B) and 5µg/kg (C) dose to healthy adult surgery patients or healthy volunteers. The grey lines represent 10 simulated individual trials and the solid black line is the mean of virtual population.

Results (ct'd)

Table 1. Clinical trial information

Age groups	Age range (yrs)	Number of subject	Male/Female numbers	Dose (route)	Regimen	Comments
Adults	50~65	10	4/6	150µg, IV	Single	Surgery
Adults	27~45	6	6/0	3µg/kg, IV	Single	Healthy volunteers
Adults	22~64	10	7/3	5µg/kg, IV	Single	Surgery
Adolescents	10~15	6	NA	5µg/kg, IV	Single	Surgery
Adolescents	13~18	5	NA	15µg/kg, IV	Single	Cardiac Surgery
Children	2~9	20	12/8	2.4µg/kg, IV	Single	Surgery
Children	3~11	7	NA	15µg/kg, IV	Single	Cardiac Surgery
Infants	0.083~0.83	7	NA	15µg/kg, IV	Single	Cardiac Surgery
Infants	0.166~2	7	NA	10µg/kg, IV	Single	Cardiac Surgery
Infants	0.25~3	6	NA	15µg/kg, IV	Single	Cardiac Surgery

Figure 2. PBPK modeling performance

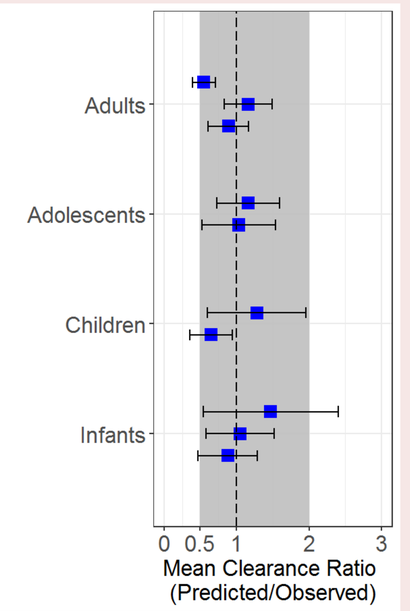
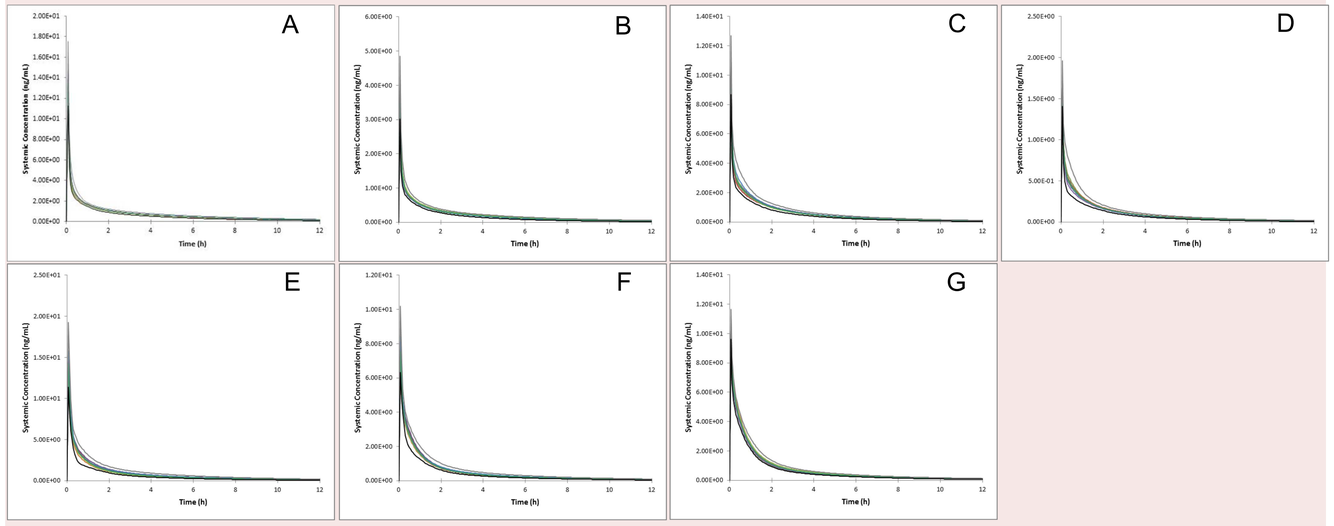


Figure 3. PBPK predicted concentration-time profile of sufentanil in pediatric patients



Mean simulated (solid line) concentrations of sufentanil after IV administration of a single dose 5µg/kg (A) and 15µg/kg (B) to adolescents, single dose 2.4µg/kg (C) and 15µg/kg (D) to children, single dose of 15µg/kg (E), 10µg/kg (F) and 15µg/kg (G) sufentanil to infants. The grey lines represent 10 simulated individual trials and the solid black line is the mean of virtual population.

Conclusions

➢ Due to the high hepatic extraction rate of sufentinal, the liver blood flow plays a dominant role in the elimination of sufentinal in both adults and pediatric patients.

➢ Developed PBPK model reasonably predicted the clearance of sufentinal across all pediatric age groups by considering ontogeny profiles of CYP3A4 and the developmental physiology built in the Simcyp pediatric model, which provides a good case example of drugs with similar properties.

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