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Introduction

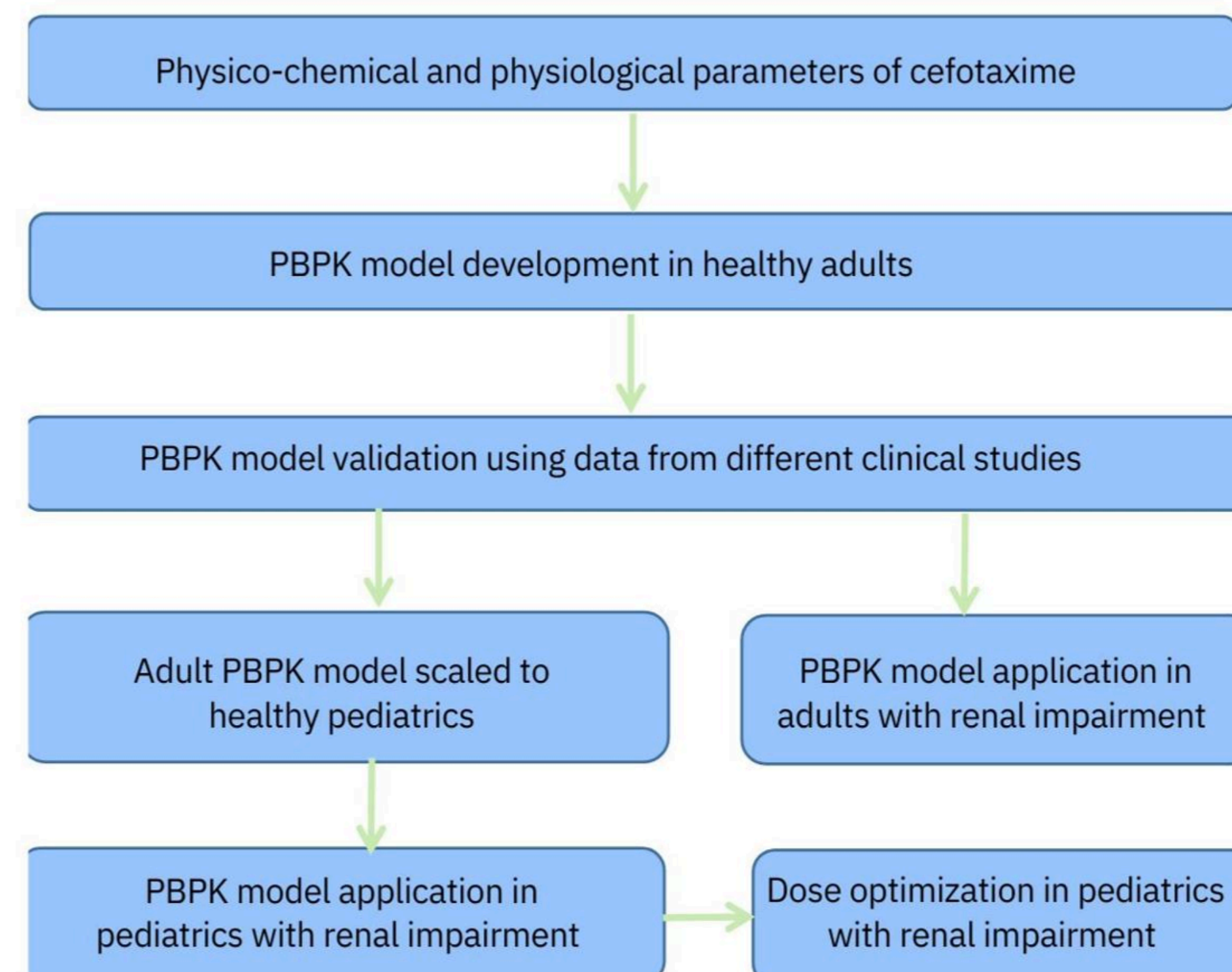
Cefotaxime is a third-generation cephalosporin, prescribed for the treatment of lower respiratory tract, central nervous system, genitourinary tract, bone and joint, intra-abdominal, and skin infections. Elimination is primarily renal, with 50-60 % of the administered dose eliminated unchanged in the urine, and 15-20 % excreted as the only known active metabolite (desacetyl cefotaxime) by Carboxylesterase 1 (CES1).

Physiological changes associated with renal impairment (RI) influences the dosing of cefotaxime in adults and children. This is because RI leads to decreased clearance (CL), likely driven by reduced transporter activity (OAT1/3), leading to increased cefotaxime internal exposure and accumulation. It is recommended to reduce the cefotaxime dose in patients suffering from severe renal impairment (RI) to avoid drug accumulation. Physiologically based pharmacokinetic (PBPK) models can predict drug disposition in special populations, which can help with decision-making for selecting dosages.

Objectives

PBPK models support dose optimization in pediatrics by accounting for age-related physiological changes and limited clinical PK data. A validated PBPK model addressing the pediatric population with impaired renal function has not yet been reported. Therefore, this study developed a GastroPlus®-based PBPK model to predict cefotaxime pharmacokinetics in children with varying renal function and support model-informed dosing recommendations.

Strategy adopted for cefotaxime PBPK modeling



Methodology

The initial PBPK model was developed using GastroPlus® software version 9.9 (Simulations Plus Inc., Lancaster, CA, USA). Km and Vmax values for OAT3 extracted from literature, included in the initial model and optimized in order to reproduce the observed plasma-drug concentration profiles. The accuracy of the model's predictions was evaluated by superimposing the observed data on predicted concentration–time curves and calculating fold error (WHO, 2010). The initial PBPK model was modified for patients with RI by incorporating a scaling factor of OAT3 Vmax, reducing glomerular filtration rate (GFR) (R. M. Ings et al., 1982) adopting the Dettli method and Intact Nephron hypothesis (Bricker, Morrin, & Kime Jr, 1960; Dettli, 1976). The qualified adult PBPK model was scaled to pediatric population by adjusting the activity of the renal transporter (OAT3) and GFR (Paap et al., 1991). Dosage recommendations for pediatric patients with RI were accomplished by utilizing the PBPK models of pediatrics with RI. Pharmacodynamic target attainment was evaluated by assessing the % T>MIC in the pediatric populations.

Results

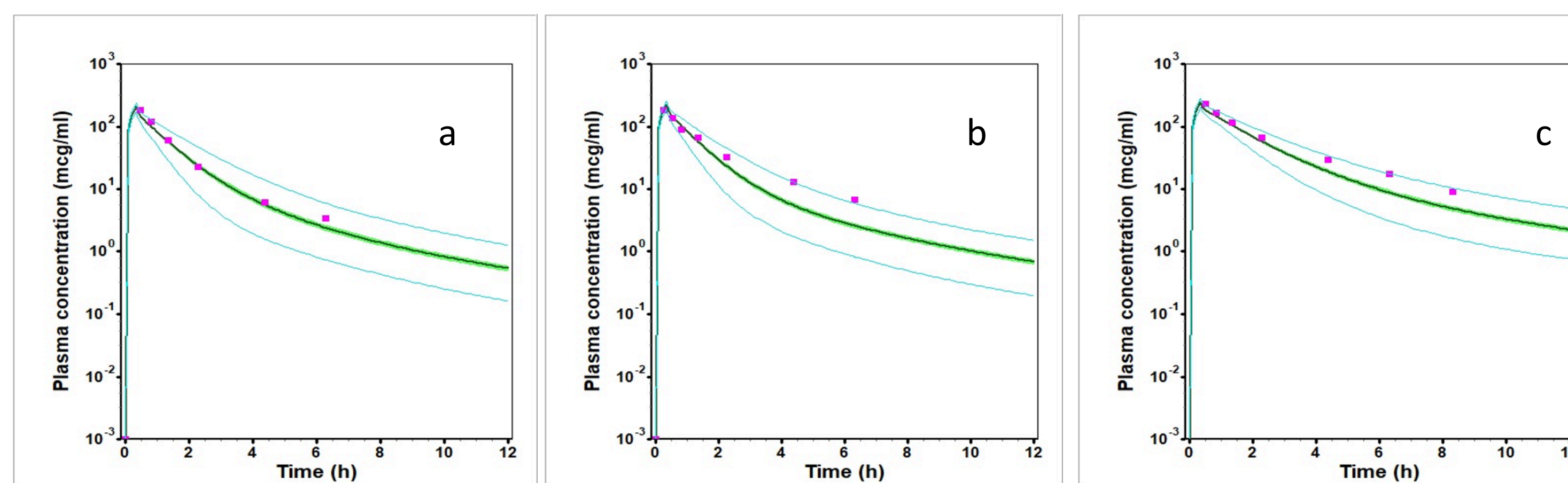
Adult PBPK cefotaxime model was successfully predicted AUC0-∞, AUC0-t, and Cmax with FE ranges between 0.5 and 2.0 (Table 1, Fig. 1). The adult PBPK model was scaled to adults with RI, and evaluation of the model in adults with RI indicates that it successfully reproduce the PK of cefotaxime in this patient population. The adult PBPK model was scaled to the pediatric population with normal renal function by incorporating age-related physiological changes and scaling renal clearance parameters, proved the prediction accuracy with fold error ranges in between 0.5 and 2. The pediatric model scaled to pediatric population with RI accurately predicted cefotaxime exposure in pediatrics with moderate and severe RI. An increase in AUC0-∞ was 1.05-fold in moderate RI and 1.93-fold in severe RI.

Table 1. Observed versus physiological based pharmacokinetic (PBPK) model-derived pharmacokinetic parameters in adults without renal impairment.

Dosages	Predicted AUC0-∞a (µg.hr/mL)	Observed AUC0-∞ (µg.hr/mL)	FEb	Predicted Cmaxc (µg/mL)	Observed Cmax (µg/mL)	FE	Reference
500 mg, IV 5 min	30.36	30.16	1.01	46.5	42.19	1.1	(Lüthy et al., 1981)
1000 mg, IV 5 min	62.74	64.15	0.98	100.35	94.99	1.06	
2000 mg, IV 5 min	128.54	150.7	0.85	201.46	176.2	1.14	

aAUC0-∞: 0 to infinity hours blood drug concentration-area under the time curve, bFE=fold error, cCmax: Peak blood concentration.

Fig. 2. Observed (pink squares) and predicted (black line) Cp-time profiles of cefotaxime following intravenous infusion (50 mg/kg in 20 min), as simulated by the PBPK model in pediatrics (Paap et al., 1991), (a) normal renal function, (b) moderate renal impairment, and (c) severe renal impairment, with 90% confidence interval (light green) and 95th percentile (turquoise).



The recommended cefotaxime dosages for pediatrics with moderate and severe RI were 35 mg/kg BW and 24 mg/kg BW, respectively. At these doses, simulation predicted attainment of pharmacodynamic targets, with 56.25% and 84.5% T>MIC for moderate and severe RI, respectively.

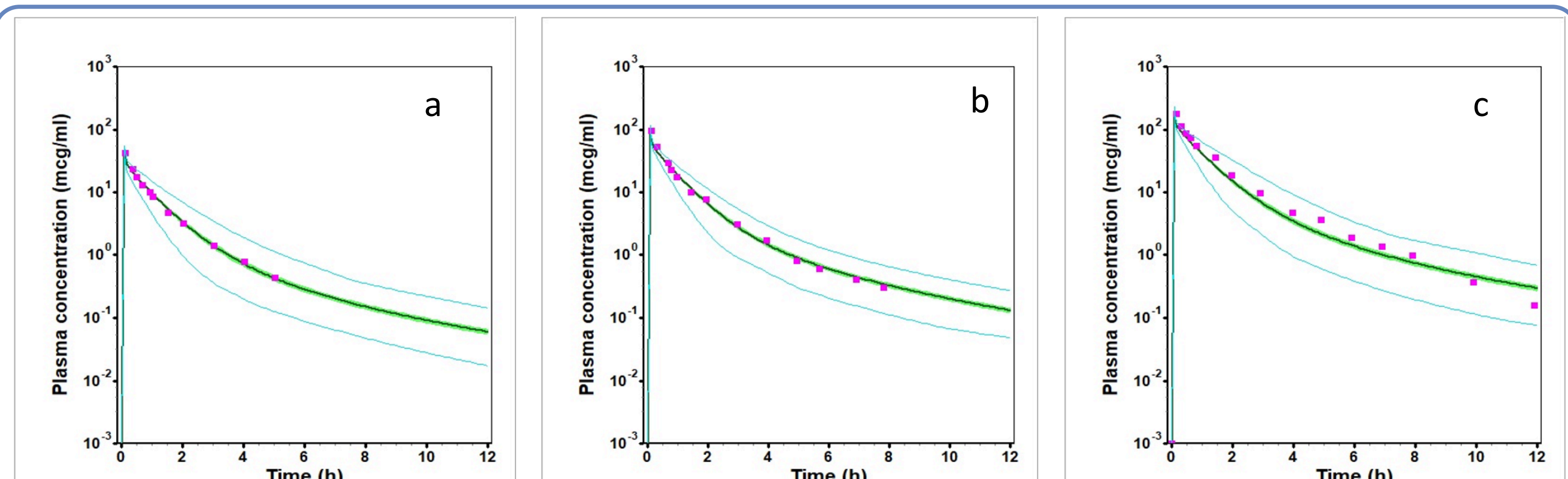


Fig. 1. Observed (pink squares) and predicted (black line) Cp-time profiles of cefotaxime following intravenous infusion (500-2000 mg in 5 min) in healthy adults (Lüthy et al., 1981), (a) 500 mg, (b) 1000 mg, and (c) 2000 mg, with 90% confidence interval (light green) and 95th percentile (turquoise).

Table 2. Dose recommendations utilizing the physiologically-based pharmacokinetic model-derived pharmacokinetic parameters in pediatric population with renal impairment.

Populations	Normal/-Renal impairment stage	Incre-ment in AUC0-∞	Percent dose reducti-on (%)a	Recomm-ended dose (mg/kg of BW)	Predicted AUC0-∞ after dose adjustment (µg.hr/mL)	%T> MICb
Pediatrics-c	Normal renal function	----	----	----	----	63.75
	Moderate renal impairment	1.05	30	35	219.79	56.25
	Severe renal impairment	1.93	52	24	265.21	84.5

aAUC0-∞: 0 to infinity hours blood drug concentration-area under the time curve, bthe percentage of time that elapses between subsequent antibiotic dosages while the antibiotic's concentration remains higher than the minimum inhibitory concentration (MIC) i.e. 4 mg/L of cefotaxime, c(Paap et al., 1991).

Conclusion

The developed model was validated to predict cefotaxime exposure in adults and pediatrics with or without RI by mechanistically accounting for changes in OAT transporter activity and GFR.

The model-informed dose reduction was proposed for children with severe RI require a dose of 24 mg/kg BW, whereas those with moderate RI require 35 mg/kg BW. For all optimized cefotaxime dosages, the 56.25-84.5%T>MIC has been attained in pediatric populations with RI. These results support the use of PBPK modeling in pediatric populations with altered physiology and demonstrate its usefulness as a tool for precision dosing.

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