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A Physiologically Based Pharmacokinetic Model of Rivaroxaban: Role of OAT3 and P-gp Transporters in Renal Clearance

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PURPOSE

Rivaroxaban is an oral anticoagulant which acts by inhibiting factor Xa of the coagulation network. It is used in the prevention and treatment of thromboembolism in patients undergoing knee or hip replacement surgery and in stroke prevention in patients with atrial fibrillation. Rivaroxaban undergoes CYP-mediated oxidative metabolism mainly via CYP3A4 with a minor contribution of CYP2J2. It is also a substrate for efflux transporter P-gp and uptake transporter OAT3 in kidney. These enzymes and transporters were incorporated in the model presented.

OBJECTIVES

The aim of this work was to develop a physiologically based pharmacokinetic (PBPK) model of rivaroxaban and explore the role of OAT3 and P-gp transporters in its renal excretion and CYP mediated metabolism. The model was applied to different populations to account for genetic changes for these populations

METHODS

A mechanistic PBPK model for rivaroxaban was developed using GastroPlus™ 9.6 (Simulations Plus, Inc.) Advanced Compartmental Absorption and Transit™ (ACAT™) model and PBPKPlus™ module were used to mechanistically explain absorption, distribution, and clearance mechanisms. The kinetic parameters (Km and Vmax) for CYP3A4-mediated metabolism were obtained from literature: CYP2J2, being a minor pathway, was not included in this model. For transporters, the values were obtained either from literature (OAT3) [1] or fitted. The model was calibrated against plasma concentration-time (Cp-time) profile after intravenous administration and with oral doses with in fasted condition, as well as with Cp-time and urinary excretion profiles after oral administration of 10 mg doses reported in literature. The model was further validated by comparing simulated and observed Cp-time profiles of rivaroxaban obtained from clinical studies reported in literature for 1.25, through 80 mg oral doses administered to Caucasian subjects. The model for the Chinese population was developed by reducing OAT3 expression in kidney 2-fold [2]. The expression level for P-gp remained the same as in Caucasian population [3]. The remaining physiological parameters, including CYP3A4 expression levels, were used as generated for Chinese subjects by built-in algorithms in GastroPlus. Physiochemical properties used for model are listed in Table 1

Table 1: Physiochemical properties of rivaroxaban

Parameter	Value	Units
Log P	1.5	
pKa (acid)	10.87	
pKa (acid)	13.6	
Solubility		
Water	7	mg/mL
FaSSIF	0.02	mg/mL
FeSSIF	0.08	mg/mL
Caco-2 Papp	7.45 E-6	cm/s
Plasma Fup	5.1	%
Blood to plasma conc ratio	1.08	

RESULTS

The in vitro Km of CYP3A4 (5.78 µM) and OAT3 (1.1 µM) were used as reported in literature [1], Km for Pgp was fixed as 10 mg/L, and all Vmax values were fitted: CYP3A4 (2.96 E-5 mg/s for gut, 4.13 E-6 mg/s/mg enz for Liver); OAT3 (1.8E-6 mg/s/mg trans), P-gp (5E-4 mg/s for gut and 1.52E-4 mg/s/mg trans for Kidney). Simulated plasma concentration-time profiles of rivaroxaban with fitted Vmax values were in close agreement with observed data across different dose levels as summarized in Table 2. Similarly the model captured rivaroxaban PK after administration of 10 mg and 20 mg doses in fasted and fed state (Figure 1 and Table 2). The validated final model was able to match the fraction of compound cleared via urinary excretion (light blue lines), ~30% of dose cleared for a 10 mg dose up to 24 hours reported in literature [4] and confirm the role of OAT3 and P-gp in urinary excretion of rivaroxaban. Our model simulated renal excretion of 24 % in fasted and 33 % in fed conditions after 24h of 10 mg PO dose of rivaroxaban.

Figure 1: Simulated vs observed concentration profiles of Rivaroxaban in Caucasian subjects in fasted (A) and fed (B) state; dark blue line -simulated plasma profile, blue squares - observed data, light blue line- percent of dose secreted in urine, pink line – percent of dose metabolized.

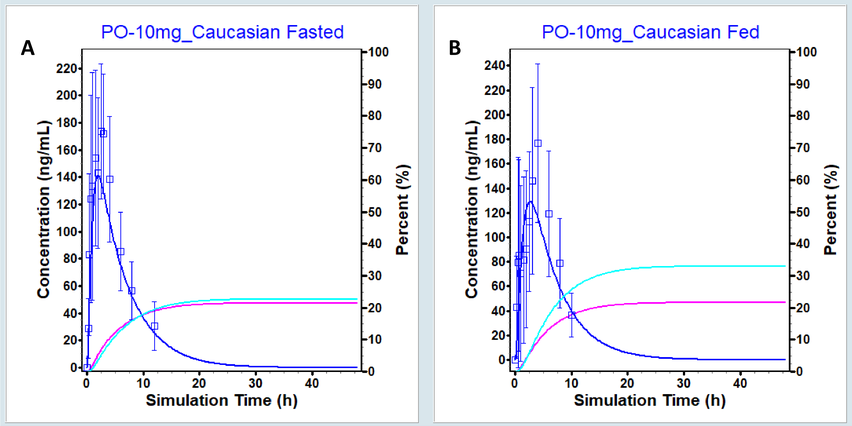

Figure 2: : Simulated vs observed concentration profiles of Rivaroxaban in Chinese subjects after administration of 10 mg (A) and 20 mg (B) dose in fasted state. The colors of lines and symbols are the same as described in Figure 1.

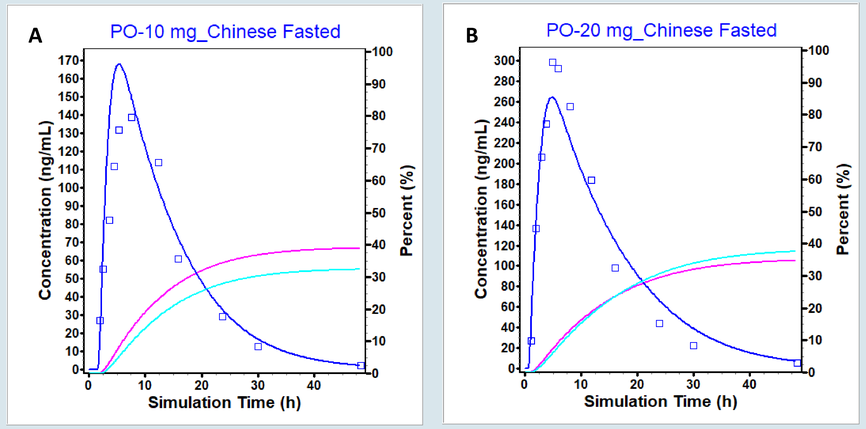

Table 2: PK parameters of Rivaroxaban in different Chinese and Caucasian population

		Observed		Predicted		Ratio (Obs/Pred)	
Population	Dose (mg)	Cmax (ng/mL)	AUC 0-inf (ng-h/mL)	Cmax (ng/mL)	AUC 0-inf (ng-h/mL)	Cmax	AUC
Chinese	5	79	1120	88	1183	0.90	0.95
	10	139	2140	168	2355	0.83	0.91
	20	298	4138	264	4344	1.13	0.95
	30	426	6147	426	6587	1.00	0.93
Caucasian Fasted	1.25	20	79	16	107	1.25	0.74
	10	174	1285	141	1032	1.23	1.25
	10	133	940	120	874	1.11	1.08
	10	158	893	118	858	1.34	1.04
	10	120	904	121	898	0.99	1.01
	10	161	841	126	912	1.28	0.92
	20	165	1508	200	1605	0.83	0.94
	20	186	1610	202	1606	0.92	1.00
	40	191	2357	299	2631	0.64	0.90
	80	287	3138	401	4256	0.72	0.74
Caucasian Fed	10	176	1123	129	1035	1.36	1.09
	20	180	1367	200	1653	0.90	0.83

CONCLUSIONS

The model was successfully applied to capture the gut and liver metabolism of rivaroxaban by CYP3A4, and renal elimination mediated by P-gp and OAT3 transporters. Chinese population showed slightly lower total clearance of rivaroxaban compared to the Caucasian population. The differences in PK between these two populations are explained by 1) lower expression levels of CYP3A4 and 2) lower expression levels of OAT3 in Chinese populations.

Rivaroxaban is significantly cleared renally, current model captures the renal CL adequately and could be potentially applied to predict rivaroxaban PK in subjects with renal impairment. Validation of the model for this application is ongoing.

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