Physiologically-based pharmacokinetic modeling of the effect of chronic kidney disease on the pharmacokinetics of drugs eliminated nonrenally

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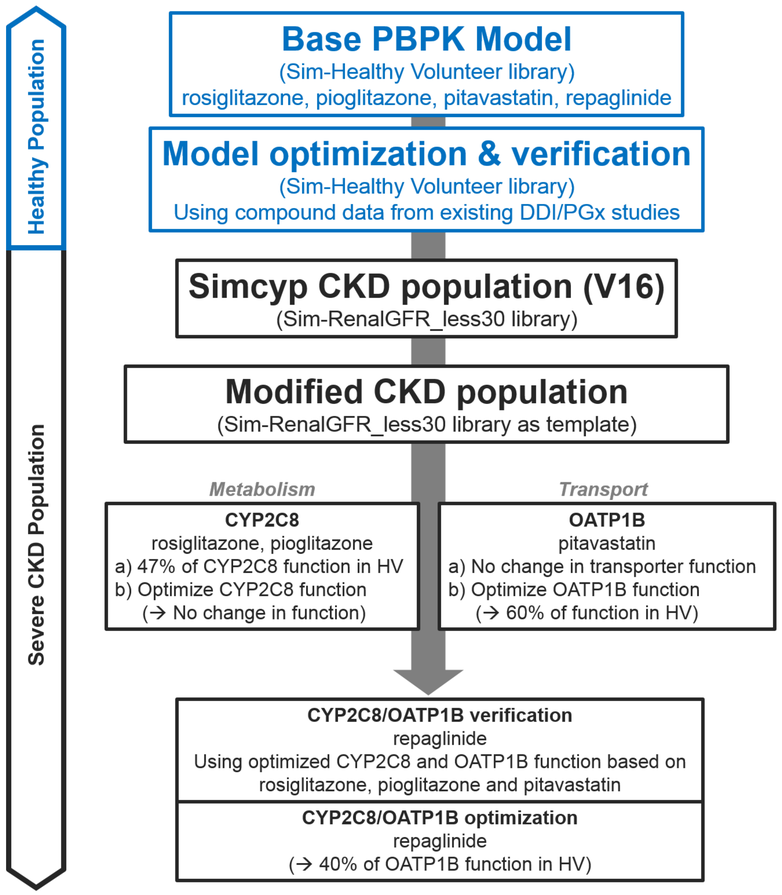
Background and Purpose

- Clinical studies have shown that chronic kidney disease (CKD) can affect the pharmacokinetics (PK) of nonrenally eliminated drugs[1]
- CKD differentially affects the PK of nonrenally cleared drugs: CYP2D6 and OATP1B-mediated clearance generally decreases as kidney function declines, but it has negligible effect on drugs cleared predominantly by CYP1A2, 2C9, 2C19 and 3A4[2,3]
- CKD effect on CYP2C8-mediated clearance is not well understood due to overlapping substrate specificity with hepatic OATP1B[3]

Purpose: Employ physiologically-based pharmacokinetic (PBPK) modeling to quantitatively evaluate potential changes in the activity for CYP2C8 and OATP1B in patients with CKD

Methods

Workflow of PBPK modeling and simulations



- **The base PBPK models were optimized and verified using clinical drug-drug interaction (DDI) and pharmacogenetics (PGx) studies in healthy volunteers (HVs)**
- **The verified models were applied to Simcyp default ("Sim-RenalGFR_less30") and modified severe (default but CYP2C8 abundance set to HVs) CKD populations for**
  1. **CYP2C8 substrates rosiglitazone and pioglitazone**
  2. **OATP1B substrate pitavastatin**
  3. **CYP2C8/OATP1B dual substrate repaglinide**

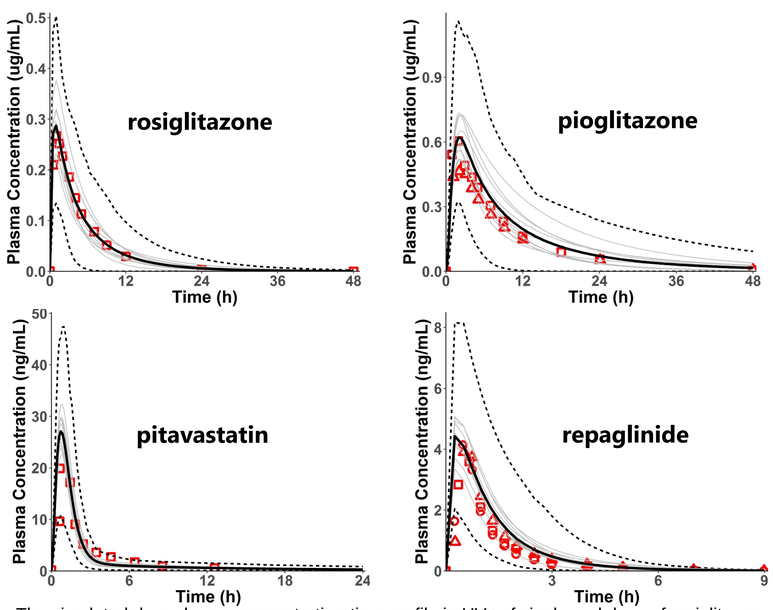
Results and Discussion

Effect of CKD on pharmacokinetics of model substrate drugs

Enzyme or transporter	Substrate Drug	CKD populations	fu* (%) HV	fu* (%) CKD	AUCR (total) Simulated	AUCR (total) Observed*	R value	AUCR (unbound) Simulated	AUCR (unbound) Observed*	R value
CYP2C8	Rosiglitazone	Simcyp (CYP2C8 47%)	0.16	0.22	1.44	0.81	1.78	2.47	1.11	2.23
		Modified (CYP2C8 100%)[a]	0.16	0.22	0.93	0.81	1.14	1.58	1.11	1.42
	Pioglitazone	Simcyp (CYP2C8 47%)	3	*3.5***	1.58	0.78	2.03	2.40	*0.92***	*2.61***
		Modified (CYP2C8 100%)[a]	3	*3.5***	0.90	0.78	1.15	1.36	*0.92***	*1.48***
OATP	Pitavastatin	Simcyp (CYP2C8 47%,OATP100%)	0.6	0.6	0.85	1.36	0.63	1.05	1.36	0.77
		Simcyp (CYP2C8 47%,OATP 60%)[b]	0.6	0.6	1.28	1.36	0.94	1.59	1.36	1.17
		Modified (CYP2C8 100%,OATP100%)	0.6	0.6	0.84	1.36	0.62	1.04	1.36	0.77
		Modified (CYP2C8 100%,OATP60%)[b]	0.6	0.6	1.28	1.36	0.94	1.59	1.36	1.17
CYP2C8/OATP	Repaglinide	Simcyp (CYP2C8 47%,OATP100%)	3.6	3.6	1.37	2.72	0.51	1.72	2.72	0.63
		Simcyp (CYP2C8 47%,OATP 50%)[b]	3.6	3.6	2.55	2.72	0.94	3.18	2.72	1.17
		Modified (CYP2C8 100%,OATP100%)	3.6	3.6	1.08	2.72	0.40	1.35	2.72	0.50
		Modified (CYP2C8 100%,OATP60%)	3.6	3.6	1.72	2.72	0.63	2.14	2.72	0.79
		Modified (CYP2C8 100%,OATP45%)	3.6	3.6	2.20	2.72	0.81	2.75	2.72	1.01
		Modified (CYP2C8 100%,OATP40%)[b]	3.6	3.6	2.43	2.72	0.89	3.03	2.72	1.11

Simcyp default and modified "Sim-RenalGFR_less30" severe renal impairment populations were used in the simulations with GFR, average age, and gender matched to the corresponding clinical CKD studies. The CYP2C8 abundance was reduced to 47% of HV in Simcyp default "Sim-RenalGFR_less30". The CYP2C8 abundance was set back to 100% of HV in the "modified" Sim-RenalGFR_less30 population. [a]CYP2C8 or OATP1B abundance as in HV; [b]OATP1B function was optimized to reproduce the observed AUCR. HV: healthy volunteers. *Observed fu[3]. **Estimated fu[3].

No need to decrease CYP2C8 activity for substrates rosiglitazone and pioglitazone, while up to 60% reduction of OATP1B activity for substrates pitavastatin and repaglinide was needed to recover the observed PK changes in patients with CKD.



The simulated drug plasma concentration-time profile in HVs of single oral dose of rosiglitazone (4 mg), pioglitazone (15 mg), pitavastatin (2 mg) and repaglinide (0.25 mg). The solid lines are the simulated mean values, dotted lines are the 5th and 95th percentiles and grey lines are for different trials. Data points are observed values from different studies.

Base models were optimized and verified to reproduce the clinical observation in healthy subjects

Conclusions

- **The PBPK analysis suggests that negligible change in CYP2C8 enzyme function was required to match the observed AUC changes in severe CKD patients.**
- **Decrease in OATP1B activity of up to 60% was needed to recover the observed AUC change in severe CKD patients.**
- **CYP enzyme and transporter interplay can be modeled and simulated through PBPK modeling.**

References

1. Yeung *et al.,* Kidney International. 2014; 85:522.
2. Yoshida *et al,* Clin. Pharmacol. Ther. 2016; 100:75.
3. Tan *et al,* Clin. Pharmacol. Ther. 2017; http://onlinelibrary.wiley.com/doi/10.1002/cpt.1807/epdf

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