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Quantitative Prediction of Renal Transporter-Mediated Clinical Drug–Drug Interactions

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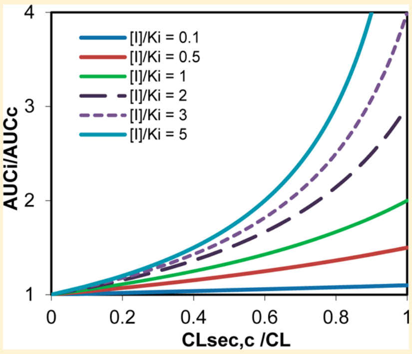
Ⓢ *Supporting Information*



ABSTRACT: Kidney plays a critical role in the elimination of xenobiotics. Drug–drug interactions (DDIs) via inhibition of renal organic anion (OAT) and organic cation (OCT) transporters have been observed in the clinic. This study examined the quantitative predictability of renal transporter-mediated clinical DDIs based on basic and mechanistic models. *In vitro* transport and clinical pharmacokinetics parameters were used to quantitatively predict DDIs of victim drugs when coadministrated with OAT or OCT inhibitors, probenecid and cimetidine, respectively. The predicted changes in renal clearance (CL_r) and area under the plasma concentration–time curve (AUC) were comparable to that observed in clinical studies. With probenecid, basic modeling predicted 61% cases within 25% and 94% cases within 50% of the observed CL_r changes in clinic. With cimetidine, basic modeling predicted 61% cases within 25% and 92% cases within 50% of the observed CL_r changes in clinic. Additionally, the mechanistic model predicted 54% cases within 25% and 92% cases within 50% of the observed AUC changes with probenecid. Notably, the magnitude of AUC changes attributable to the renal DDIs is generally less than 2-fold, unlike the DDIs associated with inhibition of CYPs and/or hepatic uptake transporters. The models were further used to evaluate the renal DDIs of Pfizer clinical candidates/drugs, and the overall predictability demonstrates their utility in the drug discovery and development settings.

KEYWORDS: *renal transporters, drug–drug interaction, renal clearance, probenecid, cimetidine*

■ INTRODUCTION

Kidney plays a key role in the excretion of endogenous and exogenous substances, and its importance in the elimination of drugs has been well-studied. A recent analysis of 391 compounds with clinical data suggested about 31% of compounds are predominantly eliminated in urine (i.e., renal clearance accounted for more than 50% of total body clearance), underscoring the significance of renal clearance in drug exposure.[1] Renal clearance is the net result of passive and active processes, including glomerular filtration, passive tubular reabsorption, and carrier-mediated transport mechanisms involved in the active secretion and tubular reabsorption.[2] Glomerular filtration rate is primarily determined by the plasma protein binding and needs to be considered in assessing the contribution of active secretion to net renal clearance.

Kidney has developed complex high-capacity transport systems at the proximal tubules to retain nutrients in the body, and simultaneously to facilitate secretion of a wide range of endogenous substances and xenobiotics. The secretory process is predominantly controlled by the Solute Carrier Family 22A (*SLC22A*) transporter system, which includes organic anion transporters (OATs) and organic cation transporters (OCTs).[3] These transporters, with broad substrate specificities, are located at the basolateral membrane of the proximal tubular cells and facilitate the secretion of drugs from the blood into urine. Most hydrophilic acids and bases yield net renal secretion in the clinic,[1] suggesting that ionization and hydrophilicity are important determinants of the affinity for the secretory transport systems.[4,5] Renal OAT1 and OAT3 are mainly involved in secretion of anionic drugs including enalapriat, furosemide, and acyclovir, and so forth. Meanwhile, renal OCT2 mainly transports cationic drugs such as antihistamines, antiarrhythmics, antibiotics, β-adrenoceptor blocking agents, cytostatics, and sedatives.[3]

Besides renal uptake transporters expressed on the basolateral membrane of proximal tubules, drug efflux pumps, including P-glycoprotein (P-gp), breast cancer resistance

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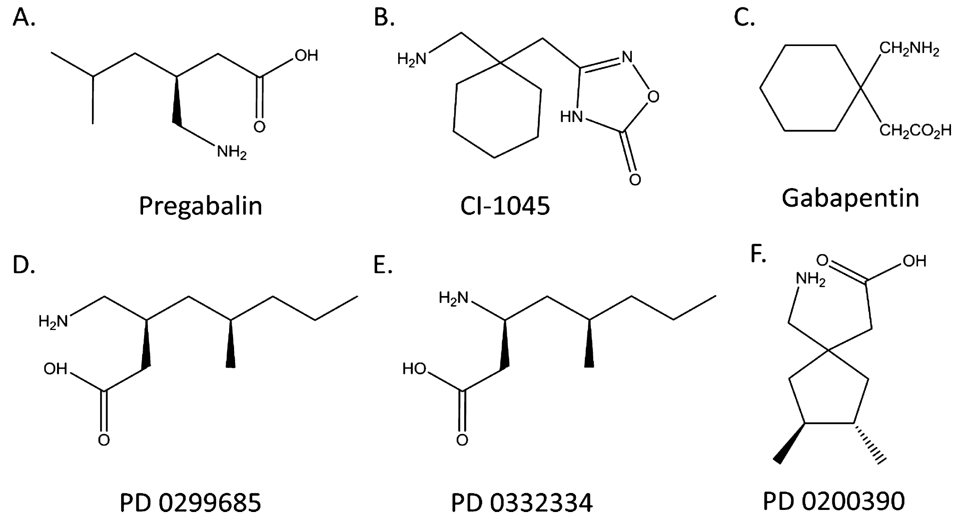

Figure 1. Chemical structures of Gapabentin, Pregabalin, CI-1045 and three $\alpha 2\delta$ compounds, including PD 0200390, PD 0299685, and PD 0332334.

protein (BCRP), and multidrug resistance associate protein 2 and 4 (MRP2 and MRP4), have been identified on the brush border of renal proximal tubules.[6] In addition, organic cation/carnitine transporter including OCTN1 and OCTN2, and multidrug and toxin extrusion transporters (MATEs) including MATE1 and MATE2-K, are expressed in the apical side of renal proximal tubular cells, and mediate the renal secretion of organic cations.[7] Additionally, other transporters at the proximal tubules, such as peptide transporter 2 (PEPT2) and system L amino acid transporter (LAT1), and so forth, may contribute to the active renal reabsorption process. However, clinical relevance of these transporters in the renal disposition is not fully understood.

Renal uptake transporters, OATs and OCTs, are known to be associated with clinical drug−drug interactions (DDIs). Probenecid inhibits OATs-mediated renal transport of β-lactams, ACE inhibitors, and antiviral drugs, leading to a significant decrease in their renal clearance while increasing the plasma exposure.[8] It was also reported that coadministration of probenecid led to an increased elimination half-life and an elevated the area under the plasma concentration−time curve (AUC) of methotrexate, an anticancer drug mainly renally cleared through OAT-mediated active secretion.[9] Similarly, OCT2 inhibitors, such as cimetidine, are known to reduce the renal clearance of several cationic drugs including metformin, procainamide, levofloxacin, and dofetilide.[8] These examples suggest that concomitant use of OAT or OCT substrates and inhibitor drugs should be carefully monitored for a decrease in renal clearance and increase in systemic exposure. Therefore, further mechanistic understanding and clinical evidence are warranted to put inhibition of renal apical efflux transporters in context for drug interactions.

Renal DDI risk assessment requires an understanding of the transport kinetics of the substrate and inhibition potency (IC_{50} or K_i) of the coadministered inhibitor, in the context of clinically relevant exposures. Various *in vitro* studies, especially the transporter-transfected cell culture models, are now being used as screening tools for determining the potential of compounds to be transporter substrates and inhibitors and provide the basis for designing subsequent *in vivo* DDI studies. However, the quantitative predictability of renal DDIs using *in vitro* data was not comprehensively evaluated.

In this study, we evaluated the factors determining the extent of renal DDIs and assessed the quantitative predictability of renal DDIs based on two static models, a basic and a mechanistic model. Inputs for these models included transport kinetic parameters of substrate ("victim") and inhibitor ("perpetrator") drugs obtained from *in vitro* transport studies and the clinical pharmacokinetics data. Finally, we outlined the strategy and considerations in evaluating clinical renal DDIs of new chemical entities (NCEs).

■ MATERIALS AND METHODS

Materials. PD-0200390, PD-0299685, PD-0332334, CI-1045, Gabapentin, and Pregabalin (Figure 1) were synthesized at Pfizer Global Research and Development (Groton, CT). All other drugs were purchased from Sigma-Aldrich (St. Louis, MO).

Cell Culture. All renal transporter cell lines were cultured according to the procedures reported earlier.[10] Briefly, HEK293 cells were cultured in Dulbecco's modified Eagle's medium (DMEM), 10% heat inactivated fetal bovine serum (FBS), 1% penicillin−streptomycin, and 100 mg/mL zeocin. Transporter stably transfected HEK293 cells, hOCT2-HEK, hOCTN1-HEK, hOCTN2-HEK, hOAT1-HEK, and hOAT3-HEK, were cultured in DMEM containing 10% FBS, 1% gentamicin, and 50 mg/mL hygromycin.

Transporter Substrate Assays. The assays were carried out according to the procedures reported earlier.[10] Briefly, nearly confluent cells were seeded in 24-well poly-D-lysine-coated plates 48 h before each experiment. Immediately before the experiment, the cells were washed twice with 1 mL of Dulbecco's phosphate-buffered saline (DPBS) buffer at room temperature and then incubated with 100 μL of DPBS buffer containing test compound at 37 °C. After 5 min, the cellular uptake was terminated by washing the cells three times with 1 mL of ice-cold DPBS and then lysed in the presence of 1% sodium dodecyl sulfate. Time course studies suggested linear uptake within 5 min (data not shown). Radioactivity in each sample was quantified using liquid scintillation counter. For cold compounds, the cellular uptake was terminated after 5 min by washing the cells three times with 1 mL of ice-cold DPBS and then lysed directly on the plate in the presence of

Table 1. Observed and Predicted Renal Clearance Reduction of Organic Anionic Drugs from Probenecid[a]

victim	victim renal clearance, control (mL/min)	fu × GFR (mL/min)	observed renal clearance with probenecid (mL/min)	observed renal clearance reduction (%)	predicted renal clearance reduction (%)	reference
acyclovir	248	102	168	32	44	27
bumetanide	145	1.20	22.0	85	74	28
cefamandole	229	30.0	57.0	75	65	29
cefmenoxime	159	72.0	66.0	58	41	30
cidofovir	151	113	95.7	37	19	31
cimetidine	360	97.2	270	25	55	32
cinoxacin	153	36.0	66.0	57	57	33
ciprofloxacin	373	72.0	134	64	61	34
enalapril	229	54.0	61.0	73	57	35
enalaprilat	108	74.4	66.0	39	23	35
famotidine	297	96.0	107	64	51	17
fexofenadine	230	42.0	74.0	68	61	36
furosemide	72.8	1.68	20.3	72	73	37
ganciclovir	235	119	190	19	37	38
nafcilin	141	12.0	39.2	72	69	39
oseltamivir	262	116	125	52	42	40
zalcitabine	310	115	180	42	47	41
zidovudine	333	90.0	209	37	55	42

[a] All of the predictions were based on the assumption that probenecid can inhibit 75% of active secretion of victim drugs, and no transporter-mediated reabsorption is involved.

methanol. The compound concentration in each sample was quantified by LC/MS/MS methodology.

When compounds with amino acid structures were tested in the renal transporter substrate assays, BCH (2-aminobicyclo-[2,2,1]-heptane-2-carboxylic acid), an selective inhibitor of L-type amino acid transporter was used to inhibit the endogenous amino acid transporter activity in the renal transporter-transfected cell lines.[11] Therefore, the ability of the test compound to be transported by renal transporters can be studied separately without the interactions with amino acid transporters.

Transporter Inhibition Assays. The assays were carried out according to the procedures reported previously.[10] Incubations were performed in 24-well poly-D-lysine-coated plates using radiolabeled substrate and different concentrations of unlabeled testing compound in DPBS buffer applied simultaneously to the cells. After 5 min, the cellular uptake was terminated by washing the cells with ice-cold DPBS and then lysed in the presence of 1% sodium dodecyl sulfate. Radioactivity in each sample was quantified using liquid scintillation counter. One set was reserved as the control, in which substrate uptake was measured alone. The mean and SD of substrate uptake rate were calculated for each set ($n = 3$). These values were then converted to % uptake relative to the control (substrate uptake without inhibitor), with the control representing 100%.

Sample Analysis. *Radiolabeled.* When radioactive compounds were used for tracing, radioactivity was quantified with a Packard Tri-Carb 2900TR (Waltham, MA) scintillation counter.

LC-MS/MS Detection. Similar LC-MS/MS detection method was used as reported previously.[12] LC-MS/MS analysis was conducted on a Sciex Triple Quad 400 mass spectrometer (turbospray ionization source) with a Shimadzu LC-10 HPLC system and Gilson 215 autosampler. The mass spectrometer was controlled by Analyst 1.4.2 software. The Gilson autosampler was independently controlled by Gilson 735 software and synchronized to Analyst via contact closure. The HPLC method consisted of a step gradient with 25 μL samples loaded onto a 1.5 × 5 mm Showadenko ODP 13 μm particle size column using 95% 2 mM ammonium acetate, 2.5% methanol, and 2.5% acetonitrile. Samples were eluted with 10% 2 mM ammonium acetate, 45% methanol, and 45% acetonitrile.

Predicting Renal DDIs Using Static Models. Two static models, basic and mechanistic, with distinct levels of complexities were employed to predict the impact of perpetrators on the exposures of victims. The basic model accounts for the inhibitory effect of a perpetrator at the high end of clinical relevant exposure range to predict the change in renal clearance of the victim drug. A comprehensive mechanistic model was developed to examine the effect of inhibition of renal secretion transporters on plasma exposures of victim drug. This is principally similar to Rowland–Matin equation[13] proposed for prediction of CYP-related DDIs. The mechanistic model takes into consideration the importance of renal clearance relative to the total clearance of a victim and the variation of a perpetrator's concentration to predict the change in AUC of the victim. The AUC of victim drug in the presence (AUC_i) and absence (AUC_c) of inhibitor drug can be described as in equation. (Derivations of the model are given in the Supporting Information).

$$\frac{AUC_i}{AUC_c} = \frac{CL}{CL_i} = \frac{1 + \frac{CL_{sec,c}}{CL_x}}{1 + \frac{CL_{sec,c}}{CL_x} \times \frac{1}{1 + ([I]/K_i)}} = \frac{1}{1 - \frac{CL_{sec,c}}{CL} \times \frac{([I]/K_i)}{1 + ([I]/K_i)}}$$

where CL and CL_i are total systemic clearance in the absence and presence of inhibitory drug, respectively. $CL_{sec,c}$ represents secretory clearance in control (where no inhibitor is present), CL_x represents nonsecretory clearance ($CL_x = CL - CL_{sec,c}$), and I and K_i are maximum plasma concentration and the inhibition potency of the inhibitor drug, respectively.

Table 2. Observed and Predicted Renal Clearance Reduction from Drug−Drug Interaction with Cimetidine[a]

victim drug	victim renal clearance, control (mL/min)	fu × GFR (mL/min)	observed renal clearance with cimetidine (mL/min)	observed renal clearance reduction (%)	predicted renal clearance reduction (%)	reference
acyclovir	349	102	273	22	35	43
amiloride	358	72.0	299	16	40	44
cephalexin	263	103	208	21	30	45
dofetilide[b]	274	43.2	238 or 184	13−33	42	46
fexofenadine	230	42.0	152	34	41	47
metformin[c]	728	120	403	45	42	48
	527	120	378	28	39	49
procainamide[d]	466	101	297	36	39	50
	202	101	130	36	25	51
	347	101	196	43	35	52
ranitidine	326	102	244	25	34	45
varenicline	133	97.2	100	25	13	10
zidovudine	478	90.0	210	56	41	53

[a] All of the predictions were based on that cimetidine can inhibit about 50% of active secretion of victim drugs, and no transporter-mediated reabsorption is involved. [b] Dofetilide with cimetidine at 100 mg b.i.d. for 4 days or at 400 mg b.i.d for 4 days. [c] Metformin with cimetidine at 400 mg b.i.d. for 6 days or 5 days. [d] Procainamide with cimetidine 300 mg q.i.d. for 4 days, 3 days, or 400 mg and 200 mg every 4 h up to 12 h.

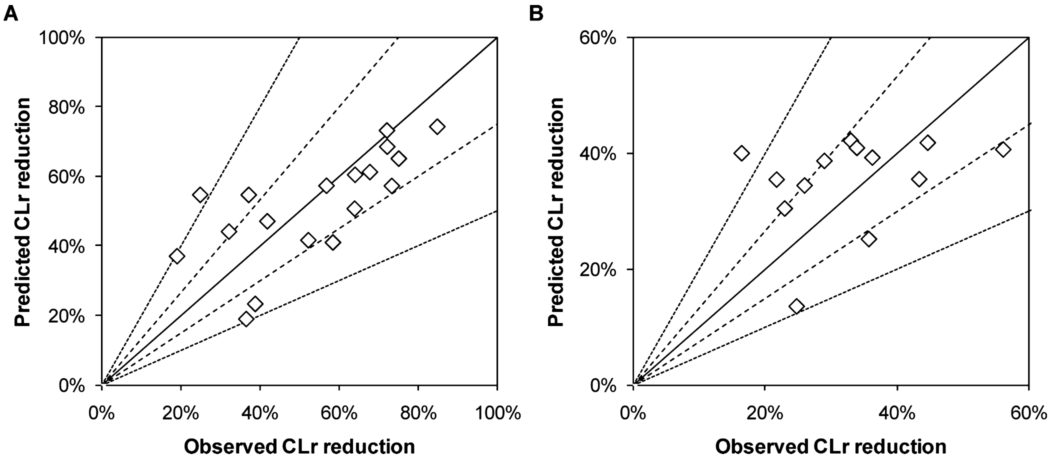

Figure 2. Performance of basic model in predicting the renal clearance change of victim drugs, when codosed with OAT1 and OAT3 inhibitor, probenecid (A), and with OCT2 inhibitor, cimetidine (B). With probenecid, modeling predicted 11 of 18 (61%) cases within 25% and 17 of 18 (94%) cases within 50% of the observed CL_r change. With cimetidine, 8 of 13 (61%) cases were within 25%, and 12 of 13 (92%) cases were within 50% of the observed CL_r change. Dashed and dotted lines represent 25% and 50% error, respectively.

■ RESULTS

Basic Model Predictions. Literature was mined to extract the clinical renal DDI data (Tables 1 and 2). The most pronounced renal DDIs reported with organic anions were caused by probenecid, presumably due to its high oral dose leading to high plasma exposure, and potent intrinsic inhibitory activity on OATs. Probenecid exhibits potent inhibition against hOAT1 and hOAT3 with *in vitro* K_i values of 12 and 9 μM, respectively.[14] At the clinical oral dose of 500−2000 mg, probenecid reaches unbound plasma concentrations ($C_{max,u}$) in the range of 3−50 μM,[15] suggesting that both hOAT1 and hOAT3 are likely to be inhibited by probenecid *in vivo*. The extent of inhibition can be estimated using the Hill equation: % inhibition = 100 × conc./(conc. + IC_{50}), with $E_o = 0$, $E_{max} = 100$, and assuming a Hill coefficient of 1. With the average $C_{max,u}$ at the clinical oral doses being ~25 μM, probenecid likely inhibits ~75% of the OATs-mediated transport functions. Considering the above inhibition potency, change in renal clearance of a victim drug can be predicted, as illustrated with famotidine. Famotidine is a substrate of hOAT3 (but not a substrate of hOAT1 or hOCT2),[16] with plasma fraction unbound (fu) and mean renal clearance (CL_r) of 0.80 and 297 mL/min, respectively.[17] Considering the average human glomerular filtration rate (GFR) of 120 mL/min, the renal filtration clearance (CL_f) of famotidine was estimated to be: fu × GFR = 96 mL/min (0.8 × 120 mL/min). Further, assuming no or negligible renal reabsorption, the OAT3-mediated secretion clearance of famotidine can be obtained from the difference between CL_r and CL_f (201 mL/min). Hence, CL_r of famotidine when coadministrated with probenecid can be expressed as: CL_f (96 mL/min) + (1 − 75% inhibited) × secretion clearance (25% × 201 mL/min) = 146 mL/min. The predicted CL_r decrease with probenecid is 51% [(297 mL/min − 146 mL/min)/297 mL/min], which is reasonably similar (within ± 25% error) to the observed CL_r decrease of about 64%.[17] Similarly, the predicted renal clearance reduction with probenecid coadministration was calculated for a set of victim drugs with clinical DDI data (Table 1). The compounds were selected based on their significant renal DDIs observed *in vivo*. Overall, this basic model reasonably predicted the change in CL_r of OATs substrates, when concomitantly dosed with probenecid (Figure 2A). The predictions for 11 of 18 (61%) cases are within 25% error, and 17 of 18 (94%) cases are within

50% error of the observed CL_r change. Complementing the literature reports, our studies using OAT1 or OAT3 transfected-cell lines suggested that all the victim drugs in Table 1 are OAT1 and/or OAT3 substrates *in vitro*.

On the other hand, the majority of the clinical renal DDIs with organic cations were caused by cimetidine, and similarly, the compounds were selected based on their significant renal DDIs observed *in vivo* (Table 2). Cimetidine, at doses of 800–1200 mg/day, inhibited the CL_r of amiloride, ranitidine, procainamide, quinidine, metformin, zidovudine, and triamterene with a percent renal clearance inhibition, ranging from 16% to 62%.[8] The *in vivo* interaction observed with cimetidine is presumably due to its high affinity for the OCTs, and the large daily doses allowing for sufficiently high circulating plasma concentrations. A 800–1200 mg/day dose will generate mean $C_{max,u}$ of ~4–12 μM,[18,19] whereas the K_i values of cimetidine ranged from 8.6 to 73 μM.[18] Given the large variability of *in vitro* inhibition data, and to avoid under-prediction of renal DDIs in the clinic, it is prudent to compare the lowest K_i (8.6 μM) with the clinic $C_{max,u}$ (12 μM) as the worst case scenarios. Thus, we estimated that cimetidine is able to inhibit about 50% of OCT2-mediated renal secretion, based on the Hill equation as discussed before. Using the basic model described here, the renal clearance reduction by cimetidine was predicted for a set of organic cationic drugs (Table 2). The predicted changes (Figure 2B) for 8 of 13 (61%) cases were within 25% and 12 of 13 (92%) cases within 50%, of the observed CL_r change. Additionally, all of the victim drugs listed in Table 2 were identified as OCT2 substrates in the *in vitro* transporter studies (data not shown). Overall, this model quantitatively predicted renal DDIs of the victim drugs when coadministered with probenecid or cimetidine.

Mechanistic Model Predictions. A comprehensive mechanistic model was developed to predict the change in the AUC of the victim drug in the presence of an inhibitor of a secretory transporter. The comparison of mechanistic model-based predictions of AUC ratios and the observed AUC ratios of organic anions codosed with probenecid is presented in Figure 3. The mechanistic model predicted 7 of 13 (54%) cases within 25% and 12 of 13 (92%) cases within 50% of the observed AUC ratios. Additionally, model simulations indicated that the predicted AUC ratio increases with increase in $[I]/K_i$ and the contribution of secretory clearance to total clearance ($CL_{sec,c}/CL$) (Figure 4).

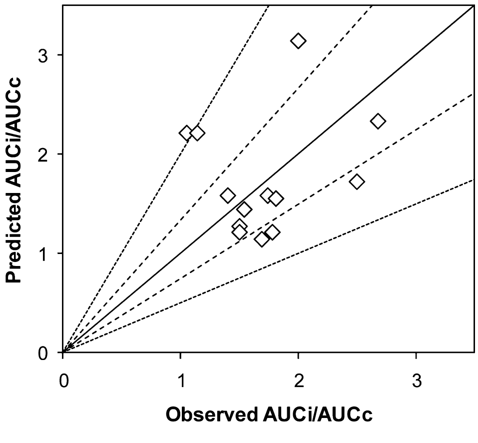

Figure 3. Comparison of the observed and predicted AUC ratios for compounds in Table 1 using mechanistic renal DDIs model with probenecid being the inhibitor of $[I]/K_i$ = 3. AUC_i is AUC with probenecid, and AUC_c is control AUC without probenecid. The mechanistic model predicted 7 of 13 (54%) cases within 25% and 12 of 13 (92%) cases within 50% of the observed AUC ratios.

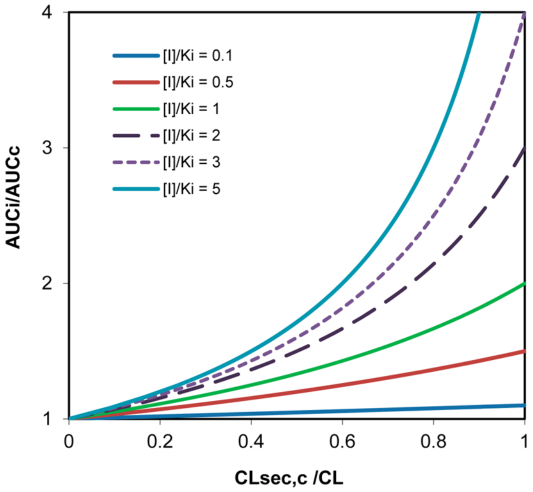

Figure 4. Mechanistic model-based predictions of AUC ratio as a function of renal CL_{sec}/CL at various $[I]/K_i$. AUC_i is AUC with inhibitor, and AUC_c is control AUC without inhibitor.

Interaction of $\alpha 2\delta$ Ligands with Renal Transporters. Pfizer novel $\alpha 2\delta$ ligands, including gabapentin, pregabalin, CI-1045, PD 0200390, PD 0299695, and PD 0332334 were tested in the major human renal transporter substrate and inhibition assays, including OAT1, OAT3, OCT2, OCTN1, OCTN2, and P-gp, to assess their potential for transporter-mediated renal DDIs (Table 3). In addition, gabapentin, pregabalin, PD 0200390, PD 0299695, and PD 0332334 were tested for substrate affinity to human amino acid transporter, LAT1, to understand the potential impact of transporter-mediated tubular reabsorption on the renal clearance. Clinical pharmacokinetic data of $\alpha 2\delta$ ligands are presented in Table 4.

In vitro renal transporter studies showed that gabapentin was a substrate of human OCT2, OCTN1 and LAT1 transporter. Similar to gabapentin, pregabalin was also identified as a substrate of OCT2, LAT1, and OCTN1. Additionally, the interaction of gabapentin and pregabalin with LAT1 transporter is consistent with the previous report.[20] CI-1045 was found to be a substrate for both OAT3 and OCTN1, and a weak inhibitor of OCTN1 with IC_{50} of 229 μM. PD 0200390 was found to be a substrate of LAT1, but not a substrate of renal secretion transporters, and PD 0200390 was a weak inhibitor of OCTN2 with IC_{50} of 333 μM. PD 0299685 was identified as a substrate of OCT2 with K_m of 569 μM and a weak inhibitor of OCTN2 (IC_{50} = 360 μM). Meanwhile, PD 0332334 was neither a substrate nor an inhibitor of human OCT2, OAT1, OAT3, OCTN1, or OCTN2, but a substrate of LAT1.

DISCUSSION

Renal transporter-mediated DDIs could lead to significant safety issues, and it has been a challenge to predict such interactions. Here, we have analyzed a set of compounds with available clinical renal DDI data and developed a basic model and a mechanistic model to predict the changes in renal clearance and the systemic exposure of the victim drug, when coadministered with inhibitors of renal transporters. Using the

Table 3. *In Vitro* Renal Transporter Substrate and Inhibition Studies of Gabapentin, Pregabalin, CI-1045, and Three $\alpha 2\delta$ Compounds, Including PD 0200390, PD 0299685, and PD 0332334[a]

	gabapentin		pregabalin		CI-1045		PD 0200390		PD 0299685		PD 0332334	
transporters	substrate (K_m, μM)	inhibitor (IC_{50}, μM)	substrate (K_m, μM)	inhibitor (IC_{50}, μM)	substrate (K_m, μM)	inhibitor (IC_{50}, μM)	substrate (K_m, μM)	inhibitor (IC_{50}, μM)	substrate (K_m, μM)	inhibitor (IC_{50}, μM)	substrate (K_m, μM)	inhibitor (IC_{50}, μM)
hOCT2	yes	>600	yes	>700	no	>1000	no	>1000	569	>1000	no	>1000
hOAT1	no	>600	no	>700	no	>1000	no	>1000	no	>1000	no	>1000
hOAT3	no	>600	no	>700	810	>1000	no	>1000	no	>1000	no	>1000
hOCTN1	yes	>600	yes	>700	652	229	no	~1000	no	>1000	no	>1000
hOCTN2	no	>500	no	>700	no	>1000	no	~333	no	369	no	>1000
LAT1	yes	340[b]	yes	184	no	ND	623	ND	weak	ND	1956	ND
P-gp	no	no[c]	no	no	ND	ND	no	no	no	no	no	no

[a] Yes = substrate, no = not a substrate, ND = not determined. If the uptake ratio (uptake in transporter transfected cell line/uptake in wild-type cell line) is above 2 when the compound is tested at 1 and 10 uM for 3 min, the compound is classified as a transporter substrate. [b] Uchino et al. *Mol. Pharmacol.* **2002**, *61*, 729−737. [c] Weiss et al. *J. Pharmcol. Exp. Ther.* **2003**, *307*, 262−267.

Table 4. Human *in Vivo* PK Data of Gapapentin, Pregabalin, CI-1045, and Three $\alpha 2\delta$ Compounds, Including PD 0200390, PD 0299685, and PD 0332334 in Healthy Volunteers or Individuals with Normal Renal Function[a]

compound	fu	CL/F (mL/min)	%AE	CL_r (mL/min)	C_{max} (μg/mL)	reference
gabapentin	>0.97	149−342	36−78%[b]	117−144	12.4	54
pregabalin	1	77.0−90.8	90%	67.0−80.9	9.1	55
CI-1045	0.79	230−323	57−100%	153−297	11.3	internal Pfizer data
PD 0200390	0.95	107−150	91−103%	105−143	2.40	internal Pfizer data
PD 0299685	0.83	130−159	81−104%	111−154	1.55	internal Pfizer data
PD 0332334	1	37.7−40.9	79−88%	30−37	28.6	internal Pfizer data

[a] fu: fraction unbound in plasma; CL/*F*: oral clearance, where CL is clearance and *F* is the bioavailability; %AE: % of dose excreted unchanged in urine; CL_r: renal clearance. The C_{max} values in the table are from a high clinically relevant dose for the marketed compounds and from the upper range of the multiple dose studies for non-marketed compounds. The clearance and AE values are from a dose range of 300 to 4800 mg/day for Gabapentin, 600 to 900 mg for Pregabablin, 5 to 200 mg for PD 0200390, 5 to 90 mg for PD 0299685, 225 to 800 mg for PD 0332334, and 25 to 1200 mg for CI-1045 (where CI-1045 exhibited dose dependent urinary excretion). Gabapentin: $CL/F = Dose/AUC_{(0\text{-}8h@steady\ state(ss))})$; $CL_r = AE_{(0-8h@ss)}/AUC_{(0-8h@ss)})$. [b] The bioavailability and thus the amount excreted unchanged in urine is dose-dependent for Gabapentin.[56]

free plasma concentration and the inhibition potency (K_i or IC_{50}) of the inhibitor, it is possible to predict the magnitude of AUC changes of a renal transporter substrate. We noted a good concordance between the predicted and the observed renal clearance changes for the victim drugs, when coadministered with typical OATs and OCT2 inhibitors, probenecid and cimetidine, respectively. Nevertheless, due to the multiplicity and complexity in the contributing processes (coexistence of filtration, secretion, and reabsorption), the models proposed here were not without certain assumptions. For example, with the obvious experimental challenges in estimating the reabsorption clearance, we assumed that the contribution of reabsorption to renal clearance is negligible. While this assumption is appropriate for hydrophilic compounds with negligible passive transport,[1,2] *in vivo* renal DDIs associated with secretory transporters could be under-predicted for compounds with significant reabsorption, with the under-estimated contribution of active renal secretion pathway. On the other hand, when drug secretion is associated with multiple transporters, the change in renal clearance may be over-predicted. Notably, the renal DDI between cimetidine and probenecid was overpredicted (Table 1), presumably due to considering inhibition of only OAT3 but not OCT2, which was suggested to also contribute to the renal active secretion of cimetidine. Regarding DDIs caused by cimetidine, it is well-documented that cimetidine not only inhibits OCT2 but also inhibits MATE1 and MATE2-K, which are expressed on the apical side of proximal tubular cells and have a similar substrate specificity as OCT2.[21] MATEs were reported to interact with organic cations including metformin, cimetidine, creatinine, and procainamide.[22] More importantly, cimetidine is a relatively more potent inhibitor of MATEs than OCT2, with K_i values against human MATE1 and MATE2-K of 1.1 and 7.3 μM, respectively.[21] Apparently, the observed cimetidine DDIs involve inhibition of OCT2, as well as MATE transporters. Consequently, it is possible that the predicted renal clearance reduction of victim drugs by cimetidine is lower than the observed renal clearance change, where MATE is involved. Overall, the predicted renal DDIs from cimetidine had a lesser clinical concordance than that from probenecid, which could be due to the functional complexity of cimetidine interactions.

We further developed a mechanistic model to predict the AUC changes associated with renal DDIs (Figure 3), and the predicted victim AUC changes with probenecid are within 50% of those reported in the clinical DDI studies. In addition, sensitivity analysis was carried out to evaluate the effect of unbound $[I]/K_i$ and CL_{sec}/CL on the magnitude of DDI (Figure 4). An important observation, based on the most potent inhibitor probenecid with an unbound $[I_{max}]/K_i$ of about 3 at the highest recommended clinical dose, was that the maximal change in exposure due to renal DDIs is expected to be no greater than 4-fold. Although, situations where unbound $[I_{max}]/K_i > 3$ could exist, they appear to be unlikely based on the existing clinical experience and the identified inhibitors with *in vitro* transporter inhibition potency so far. Additionally, the 4-fold AUC change is expected only for victim drugs with transporter-mediated secretory clearance equal to the total clearance, which is very rare. Further, for emphasis, the predicted AUC changes are based on the assumption that kidney function is normal, and it may be different in individuals with compromised renal function.

Renal transporter-mediated DDIs were assessed during the development of Pfizer novel $\alpha 2\delta$ ligands. Gabapentin and pregabalin are amino acid like, water-soluble small molecules showing negligible metabolism and low plasma protein binding, and with the amount eliminated unchanged in the urine of about 51% and 90%, respectively.[23−25] Similarly, predominant urinary elimination has been observed with other related proprietary compounds in this class, CI-1045, PD 0200390, PD 0299685, and PD 0332334. However, these compounds are diverse in their overall renal clearance characteristics (Table 4) with pregabalin and PD 0332334 showing net reabsorption, while gabapentin, PD 0200390, and PD 0299685 showed renal clearance similar to GFR, whereas CI-1045 exhibited net renal secretion in clinical studies.

To understand the renal clearance characteristics across the $\alpha 2\delta$ ligands, their interaction with renal transporters was investigated *in vitro*. Based on the transporter inhibition data (Table 3), it is unlikely that these six $\alpha 2\delta$ compounds will cause renal DDIs as a perpetrator, as the IC_{50} values are much higher than the systemic $C_{max,u}$. In addition, the risk for the six compounds to be involved in clinically relevant renal DDIs as a victim is minimal, with the exception of CI-1045. Although the major clearance pathway for the six compounds is renal clearance, the transporter-mediated renal secretion is a small component of renal clearance with CL_r/CL_f lower than 1.2, except for CI-1045. For pregabalin and PD 0332334, since CL_r is less than CL_f, transporter-mediated reabsorption process weighs more than transporter-mediated secretion pathway. Therefore, clinical interaction studies with drugs that interfere with tubular secretion were not necessary. Whereas renal clearance of gabapentin is similar to GFR, thus the contribution of active secretion to renal clearance of gabapentin is small. Consistently, gabapentin was evaluated in clinical studies for interactions with cimetidine and probenecid; cimetidine reduced gabapentin renal clearance by only ~12%, and probenecid showed no effect. These findings are aligned with the *in vitro* results where gabapentin was found to be a substrate of OCT2 but not for OATs. Similarly, the renal clearance of both PD 0200390 and PD 0299685 is similar to renal filtration clearance, which suggests the transporter-mediated renal secretion and/or renal reabsorption do not have *in vivo* significance in its renal disposition or they are in balance with neither being dominant. However, renal clearance of CI-1045 was about 2.5-fold of CL_f indicating that renal active tubular secretion contributed to at least 60% of renal clearance. Based on *in vitro* renal transporter assessment, OAT3 and OCTN1 mediate the renal active secretion of CI-1045. It is known that cimetidine inhibits both OAT3 and OCTN1 with a comparable inhibition potency as OCT2, suggesting that the renal active secretion of CI-1045 would be reduced by 50% with cimetidine. Consequently, the predicted renal clearance reduction will be at least 30% if no reabsorption is involved. In a clinical DDI study, cimetidine reduced CI-1045 renal clearance by 50%, which is consistent with that predicted from *in vitro*. With the established confidence in prediction of renal DDIs for gabapentin, pregabalin, and CI-1045, no significant renal DDIs as a victim was predicted for the other three $\alpha 2\delta$ compounds in development. Consequently, no clinical renal DDI studies were conducted for the three $\alpha 2\delta$ compounds.

After reviewing the reported clinical renal DDIs, it is apparent that the magnitude of AUC changes attributable to the renal DDIs is low (typically less than 2-fold), unlike the DDIs associated with inhibition of CYPs or/and hepatic uptake transporters, such as OATPs.[26] This is further supported by our mechanistic modeling. Although the AUC changes via the renal DDIs could be statistically significant, most of the renal DDIs have minimal clinical significance. The major attributes to the low risk of renal DDIs are the composition of multiple renal processes in renal clearance and the functional redundancy of some renal drug transporters. Furthermore, compared to a human hepatic blood flow of ~20 mL/min/kg, an exclusively renally cleared compound would have a low systemic clearance, and therefore the extent of change in the exposure due to renal DDI is considerably smaller than that with the CYPs or hepatic uptake transporter substrates. However, clinical relevance of renal DDIs needs to be evaluated in the context of efficacy and safety profile of the victim drug. Additionally, renal impairment patients have reduced renal clearance and thus need to be taken into consideration when renal DDIs are assessed.

In conclusion, we have presented a basic model and a mechanistic model to predict the extent of renal DDIs and discussed the strategy for assessing renal DDIs during drug development. The renal DDIs can be reasonably predicted based on the *in vitro* transporter interaction studies and pharmacokinetic profiles of drugs. Furthermore, we have discussed case studies where this strategy was successfully adopted to predict renal DDIs. As such, a clinically relevant renal DDI will only be observed when the involved transporter contributes significantly to the elimination pathway. Nevertheless, the inhibition potency and dose of inhibitor will determine the effect of inhibitor on the transporter function, and the PK changes of the victim drugs. Furthermore, the magnitude of change in AUC associated with renal DDI is typically low. However, awareness of the possibility of transporter-mediated DDIs is necessary for drug development. The relatively simplistic models demonstrated the ability to predict the renal DDIs *in vivo* and can aid in the development of appropriate clinical study strategies for DDI and transporter pharmacogenomics studies.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Derivations of the mechanistic model. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

OAT, organic anion transporter; OCT, organic cation transporter; MATE, multidrug and toxic compound extrusion; SLC, solute carrier family; AUC, area under the plasma concentration−time curve; DDI, drug−drug interaction; HEK, human embryonic kidney cells; DMEM, Dulbecco's modified Eagle's medium; DPBS, Dulbecco's phosphate-buffered saline; P-gp, P-glycoprotein; BCRP, breast cancer resistant protein

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