Systematic and Quantitative Assessment of the Effect of Chronic Kidney Disease on CYP2D6 and CYP3A4/5

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Recent reviews suggest that chronic kidney disease (CKD) can affect the pharmacokinetics of nonrenally eliminated drugs, but the impact of CKD on individual elimination pathways has not been systematically evaluated. In this study we developed a comprehensive dataset of the effect of CKD on the pharmacokinetics of CYP2D6- and CYP3A4/5-metabolized drugs. Drugs for evaluation were selected based on clinical drug–drug interaction (CYP3A4/5 and CYP2D6) and pharmacogenetic (CYP2D6) studies. Information from dedicated CKD studies was available for 13 and 18 of the CYP2D6 and CYP3A4/5 model drugs, respectively. Analysis of these data suggested that CYP2D6-mediated clearance is generally decreased in parallel with the severity of CKD. There was no apparent relationship between the severity of CKD and CYP3A4/5-mediated clearance. The observed elimination-route dependency in CKD effects between CYP2D6 and CYP3A4/5 may inform the need to conduct clinical CKD studies with nonrenally eliminated drugs for optimal use of drugs in patients with CKD.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ It has been reported that chronic kidney disease (CKD) can affect the pharmacokinetics of nonrenally eliminated drugs. However, there is a lack of systematic evaluation of which metabolic or transporter pathways are affected.

WHAT QUESTION DID THE STUDY ADDRESS?

☑ This study investigated elimination route dependency in the effect of CKD on nonrenal elimination pathways. For this purpose, we assessed the effect of CKD on the pharmacokinetics of *in vivo* model drugs of CYP2D6 and CYP3A4/5.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE?

☑ Although the data are limited, we observed a consistent decrease in clearance with CKD for multiple CYP2D6 model drugs, and modest but variable effect of CKD for CYP3A4/5 model drugs. In addition, it appeared that the severe CKD group may represent the "worst-case" largest exposure increase of CYP2D6 substrates.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS?

☑ Application of similar strategies to other metabolism or transport pathways can help understand whether CKD affects these pathways, and contribute to the mechanistic understandings of the effect of CKD on nonrenal elimination pathways.

Liver and kidney function are important patient-specific factors that can affect drug clearance.[1] Impaired kidney function may lead to altered systemic exposure, efficacy-safety profiles, and drug dosing requirements. Because of the growing number of patients with chronic kidney disease (CKD) in the United States,[2] it is imperative to appropriately evaluate the effect of CKD on drug exposure to optimize drug use in these patients. Both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have therefore published guidances[3,4] to recommend when and how to conduct clinical studies to determine the effect of CKD on a drug's pharmacokinetics during drug development.

Although pharmacokinetic studies with CKD patients primarily assess changes in renal elimination of drugs, it has been reported that CKD can also affect the pharmacokinetics of drugs that are cleared by nonrenal routes of elimination[5,6] that in some cases requires dose adjustment.[7] Based on these data, both the FDA and EMA currently recommend performing clinical studies of nonrenally cleared drugs in which pharmacokinetics in subjects with "worst-case scenario" CKD are compared to those of

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subjects with normal kidney function.[3,4] There are, however, differing opinions on whether dedicated CKD studies should be conducted for drugs that are cleared predominantly by nonrenal mechanisms,[8] and if such studies are conducted, what study designs should be employed.[9] Moreover, product labels for many drugs do not contain information on dose adjustment requirements in patients with impaired kidney function at the time of drug approval due to limited knowledge and uncertainty.[10]

The requirements for conducting clinical CKD studies for nonrenally eliminated drugs have not been well defined, primarily because these drugs inconsistently exhibit pharmacokinetic alterations in patients with CKD. Hence, no generalizable rules have emerged to determine when CKD studies are warranted. In addition, there is no consensus on the mechanism by which CKD may affect pharmacokinetics of nonrenally eliminated drugs. Several hypotheses have been advanced for such effects.[5,6] One is the direct inhibition of nonrenal clearance pathways, comprised largely of cytochrome P450 (CYP) enzymes, phase II enzymes (such as UDP-glucuronosyltransferase), and membrane transporters, by accumulated uremic toxins in CKD patients.[11–13] Another hypothesis is downregulation of metabolic enzymes or transporters with accumulated uremic toxins in CKD patients. Decreased protein expression, mRNA expression, and/or activity of several nonrenal clearance pathways, such as Cyp3a, Cyp2c11, Abcb1, or Mrp2, have been reported in experimental animal models of endstage renal disease (ESRD).[5] There is no direct measurement of enzyme or transporter levels or activities in humans to support this hypothesis.

Systematic assessment of the effect of CKD on individual nonrenal elimination pathways is therefore useful to increase our general understanding of the effect of CKD on nonrenally eliminated drugs. To date, the relationship between CKD and various elimination pathways has been examined for only a limited number of drugs.[7,8,14,15] We have recently developed an extensive database that allows for characterization of some of the interrelationships between impaired liver and kidney function and drug–drug interactions (DDIs) on pharmacokinetics,[16] but the database was not exhaustive with respect to CKD effects on nonrenally eliminated drugs. In the current study we compiled the available data to examine relationships between CKD and pharmacokinetics of model drugs for two elimination pathways, CYP2D6 and CYP3A4/5. Clinical DDI or pharmacogenetic data were used to determine the *in vivo* contribution of these pathways in the overall elimination of a particular drug. CYP2D6 and CYP3A4/5 were selected as the pathways of interest because a large number of marketed drugs are metabolized by these two enzymes[17] and multiple *in vivo* index inhibitors have been established.[18,19] The magnitude and overall trend in clearance changes of multiple CYP2D6 and CYP3A4/5 model drugs were evaluated in patients with CKD.

RESULTS

Clinical CKD studies for CYP2D6 and CYP3A4/5 model drugs

We identified 32 CYP2D6 model drugs and 73 CYP3A4/5 model drugs out of 937 drugs (**Figure 1**) after excluding one of 33 potential CYP2D6 model drugs and 14 of 87 potential CYP3A4/5 model drugs as described in the Methods and **Supplementary Table S1**. Thirteen of the 32 CYP2D6 model drugs (41%) had dedicated CKD studies (15 studies) (**Table 1**). Thirty-eight of the 73 CYP3A4/5 model drugs (52%) had dedicated CKD studies (46 studies, **Table 2** and **Supplementary Table S2**). Five of the CYP2D6 model drugs (16%) and 14 of the CYP3A4/5 model drugs (19%) had studies in which protein binding was measured or pharmacokinetic parameters were reported based on unbound concentrations, both in patients with CKD and healthy controls. For the CYP2D6 model drugs, these included: encainide, d- and l-nebivolol, risperidone, and drug A. For the CYP3A4/5 model drugs, these included: alfentanil, alprazolam, aprepitant, casopitant, conivaptan, eletriptan, erythromycin, maraviroc, midazolam, nisoldipine, ticagrelor, tolvaptan, silodosin, and drug C. Pharmacokinetic parameters were also collected for the CYP2D6 and CYP3A4/5 model drugs with information from CKD study reports and summarized in **Table 3**. For CYP3A4/5 model drugs, area under the concentration–time curve ratio (AUCR) attributable to hepatic CYP3A4/5 inhibition was calculated by $AUCR_{liver} = F_gAUCR$ ($\geq F_aF_gAUCR$) as described in the Methods section. The final dataset for the analysis of CYP3A4/5 consisted of 18 drugs with $AUCR_{liver} \geq 3$, where nine of them accompanied measurement of unbound drug exposure (**Table 2**).

Effect of CKD on clearance of CYP2D6 and CYP3A4/5 model drugs

Ratios of unbound clearance between various CKD groups and the normal renal function control group ($R\_CL_{unbound}$) for drugs having unbound fraction information, and ratios of clearance calculated with total (bound plus unbound) concentration (R_CL_{total}) for all drugs, were obtained from each CKD study (**Figure 2**, **Tables 1**, **2**, and **Supplementary Table S2**). Mean and range of these values are summarized in **Supplementary Table S3**. Briefly, mean $R\_CL_{unbound}$ with mild, moderate, severe CKD, and ESRD studied at off-dialysis periods were 1.16, 0.53, 0.41, and 0.50 for CYP2D6 model drugs, and were 0.84, 1.05, 0.79, and 0.99 for CYP3A4/5 model drugs, respectively. As a comparison, mean R_CL_{total} for all the drugs with CKD studies were 1.09, 0.76, 0.42, and 0.97 for CYP2D6 model drugs, and 0.85, 0.77, 0.94, and 1.03 for CYP3A4/5 model drugs, respectively. Four model drugs for CYP2D6 (d- and l-nebivolol, fluoxetine, paroxetine) and two model drugs for CYP3A4/5 (eletriptan, eplerenone) had data for mild, moderate, and severe CKD groups, and all of them showed a consistent graded decrease in R_CL according to the severity of CKD (**Figure 2**).

To interpret these observations, calculations with the following assumptions were performed. In the first calculation, we assumed a maximum of 33.3% of systemic elimination was mediated by renal clearance of parent drug, because the CYP model drugs have CYP2D6 or CYP3A4/5 contributing to a minimum of two-thirds of systemic elimination, as shown by AUCR or $AUCR_{liver}$ of ≥ 3. The theoretical lowest values for the ratios of clearance without change in nonrenal clearance were then calculated, and the calculated values of 0.88, 0.79, 0.73, and 0.67 with mild, moderate, severe CKD, and ESRD, were compared with

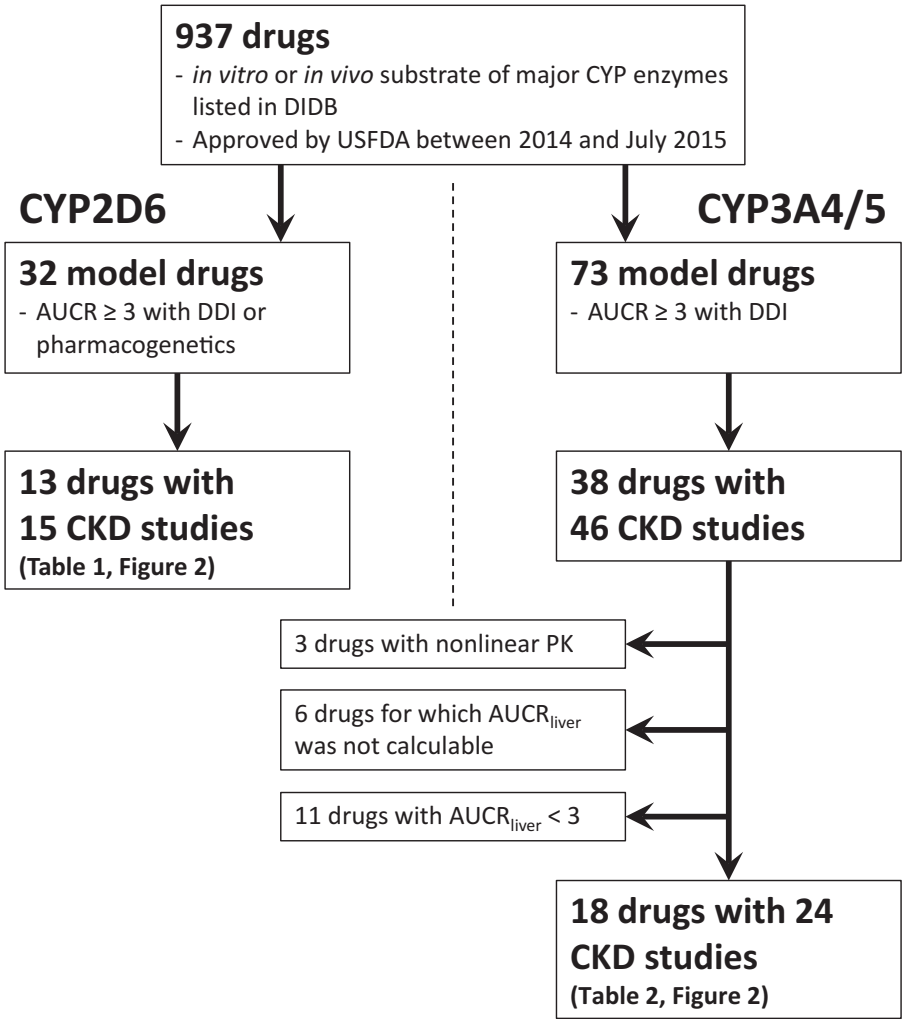

Figure 1 Overview of the workflow of clinical CKD data collection for CYP2D6 and CYP3A4/5 model drugs. AUCR, area under the concentration-time curve ratio; $AUCR_{liver}$, AUCR attributable to the inhibition of hepatic CYP3A4/5; CKD, chronic kidney disease; CYP, cytochrome P450; DDI, drug-drug interaction; DIDB, The University of Washington Metabolism and Transport Drug Interaction Database; PK, pharmacokinetics; USFDA, United States Food and Drug Administration.

observed ratios of clearance (**Figure 3**). For example, the average R_CL values with severe CKD for CYP2D6 model drugs were lower than the calculated value of 0.73, while those for CYP3A4/5 were higher than 0.73.

In the next calculation, we estimated $f_{m,CYP2D6}$ and $f_{m,CYP3A4/5}$ for each model drug from maximum AUCR or $AUCR_{liver}$ when coadministered with a strong inhibitor of the relevant pathway or AUCR in pharmacogenetic studies (**Table 3**), and calculated theoretical ratios of clearance mediated by the respective enzyme (R_CL_{CYP}). Average R_CL_{CYP} of unbound clearance between CKD groups and the healthy control group with mild, moderate, severe CKD, and ESRD studied at off-dialysis periods were 1.18, 0.54, 0.43, and 0.58 for CYP2D6 model drugs, and were 0.91, 1.21, 1.04, and 1.36 for CYP3A4/5 model drugs, respectively (**Figure 4**). Average R_CL_{CYP} of total (bound plus unbound) clearance for all the drugs with CKD studies (13 for CPY2D6 and 18 for CYP3A4/5) were 1.14, 0.83, 0.47, and 1.18 for CYP2D6 model drugs, and 0.92, 0.86, 1.22, and 1.36 for CYP3A4/5 model drugs, respectively. Similar to the result obtained from the first calculation, the average R_CL_{CYP} values with severe CKD for CYP2D6 model drugs were lower than the theoretical value of 1, while those for CYP3A4/5 were close to or greater than 1.

DISCUSSION

This study, for the first time, systematically examined the effect of CKD on multiple CYP2D6 and CYP3A4/5 model drugs with the aim of developing generalizable rules concerning the need to conduct dedicated CKD studies for nonrenally eliminated drugs. Selection of model drugs was based solely on the results of clinical DDI and pharmacogenetic studies. Effects of CYP3A4/5 inhibitors on hepatic and intestinal pathways were differentiated using indirect techniques to estimate the contribution of CYP3A4/5 to systemic elimination. Clinical CKD study reports for selected model drugs were collected and were compared to the calculated changes assuming no change in nonrenal clearance.

Our findings demonstrate that CYP2D6 model drugs show a consistent decrease in CL_{oral} (**Figures 2a,c**, **3a,c**) and in calculated CYP2D6-mediated clearance (**Figure 4a,c**) with CKD. In

Table 1 Effect of CKD on pharmacokinetics of CYP2D6 model drugs

Drugs	Parameters	Ratios of parameters with CKD					CYP2D6 activities of subjects in CKD groups	Reference
		Mild	Moderate	Severe	ESRD [a]	ESRD [b]		
		R_CL$_{unbound}$						
encainide	CL_{oral}/f_u	—	—	0.344	—	—	EM[c]	(31)
d-nebivolol	CL_{oral}/f_u	1.073	0.444	0.297	—	—	EM[d]	NDA 021742[g]
l-nebivolol	CL_{oral}/f_u	1.254	0.759	0.516	—	—	EM[d]	NDA 021742[g]
risperidone	CL_{oral}/f_u	—	0.400	0.471	—	—	—	(32)
drug A	CL_{oral}/f_u	—	—	—	0.501	—	EM[d]	—[h]
		R_CL$_{total}$						
bufuralol	CL_{oral}	—	—	0.303	—	0.205[1]	—	(33)[i]
encainide	CL_{oral}	—	—	0.218	—	—	EM[c]	(31)
fluoxetine	CL_{oral}	1.127	0.787	0.728	1.407	0.712[1]	—	(34)
metoprolol	CL_{oral}	—	1.187	—	—	0.563[2]	—	(35)[j]
	CL_{oral}	—	1.013	—	—	—	One PM subject[d]	(36)[k]
d-nebivolol	CL_{oral}	1.271	0.524	0.336	—	—	EM[d]	NDA 021742[g]
l-nebivolol	CL_{oral}	1.485	0.895	0.583	—	—	EM[d]	NDA 021742[g]
nortriptyline	CL_{oral}	—	—	—	0.867	0.766	—	(37)[j]
paroxetine	CL_{oral}	0.807	0.545	0.281	—	—	—	(38)
propafenone	CL_{oral}	—	—	—	1.006	—	EM[e]	(39)
	CL_{iv}	0.764	—	—	1.195	—	—	(40)[l]
risperidone	CL_{oral}	—	0.354	0.480	—	—	—	(32)
trimipramine	CL_{oral}	—	—	—	—	0.569	One PM subject[f]	(41)[l]
venlafaxine	CL_{oral}	—	0.788	—	0.433	—	—	(42)
drug A	CL_{oral}	—	—	—	0.897	—	EM[d]	—[h]

References after 51 can be found in the Supplementary Text S5 online. Classification of CKD subjects were based on measured urinary creatinine clearance unless otherwise noted. [a]ESRD subjects on dialysis but studied at off-dialysis periods. [b]ESRD subjects not yet receiving dialysis. [c]Determined by encainide metabolic activities to O-desmethyl and methoxy-O-desmethyl metabolites. [d]Determined by genotyping. [e]Determination method not specified. [f]Determined by dextromethorphan metabolic ratio. [g]Renal function estimated with Cockcroft and Gault equation or measured urinary creatinine clearance. [h]Data obtained from original study report submitted to USFDA. [i]Renal function estimated with creatinine clearance but calculation method not specified. [j]Renal function measured with ^{51}Cr-EDTA clearance. [k]Renal function estimated with Cockcroft and Gault equation. [l]Estimation method of renal function not specified. [1]$n = 1$. [2]$n = 2$. —, data not available. CKD, chronic kidney disease; CL_{oral}, oral clearance; CYP, cytochrome P450; EM, extensive metabolizer; ESRD, end-stage renal disease; f_u, fraction unbound in plasma; NDA, new drug application; PM, poor metabolizer; R_CL_{total}, ratio of clearance calculated with total (bound plus unbound) concentration between CKD and healthy control group; R_$CL_{unbound}$, ratio of unbound clearance between CKD and healthy control group; USFDA, United States Food and Drug Administration.

particular, all six drugs studied with severe CKD subjects showed lower $CL_{unbound}$ or CL_{total} than the lowest value calculated by assuming no change in nonrenal clearance (**Figure 3a,c**). Although CYP2D6 pharmacogenetic information was not available in all CKD studies, and genotyping results are not necessarily translatable into CYP2D6 function,[20] the aggregate clinical data suggest that CKD "impairs" CYP2D6-mediated pathways. The severe CKD group had a greater change in the clearance of CYP2D6 model drugs than the mild or moderate groups, suggesting that the severe CKD group may represent a "worst-case scenario" by causing maximum increase in exposure.

For CYP2D6 model drugs, we also observed a discrepancy between average $CL_{unbound}$ and CL_{total} in the ESRD group who are on regular dialysis but studied during an off-dialysis period, or between CL_{total} in that group and the severe CKD group. The reasons for this are unclear, because we had only one drug with $CL_{unbound}$ (drug A) and there was large variability in observed CL_{total} for different drugs. It is also plausible that, for patients undergoing dialysis, the "uremic toxins" may have been dialyzed out and therefore we did not see decreased clearance as in other groups, even the study was conducted in an off-dialysis period. In order to quantitatively evaluate such hypotheses, further studies are needed to explain the observed discrepancy and high variability in CL_{total} for the ESRD group, such as interindividual variation in protein binding.

Compared to CYP2D6 model drugs, the pharmacokinetics of CYP3A4/5 model drugs with $AUCR_{liver} \geq 3$ showed relatively smaller change with CKD (**Figures 2b,d**, **3b,d**). With severe

Table 2 Effect of CKD on pharmacokinetics of CYP3A4/5 model drugs with $AUCR_{liver} \geq 3$

Drugs	Parameters	Ratios of parameters with CKD						Reference
		Mild	Moderate	Severe	ESRD [a]	ESRD [b]	ESRD [c]	
				$R\_CL_{unbound}$				
alfentanil	$CL_{iv,u}$	—	—	—	—	—	0.703	(43)[g]
alprazolam	$CL_{oral,u}$	—	—	—	0.998	—	—	(44)[h]
	$CL_{oral,u}$	—	—	—	0.772	—	—	(45)[h]
aprepitant	$CL_{oral,u}$	—	—	0.943	1.19	—	—	(46)
casopitant	CL_{oral}/f_u	0.674	0.923	—	—	—	—	(47)
conivaptan	$(CL_{iv}\text{-}CL_r)/f_u$	0.721	1.08	—	—	—	—	(48)[i]
eletriptan	CL_{oral}/f_u	1.13	1.16	0.870	—	—	—	NDA 021016[j]
midazolam	$CL_{iv,u}$	—	—	—	—	—	1.07	(49)[g]
ticagrelor	CL_{oral}/f_u	—	—	0.831	—	—	—	(50)[i]
tolvaptan	$CL_{oral,u}$	—	1.03	0.522	—	—	—	(51)
				R_CL_{total}				
alfentanil	CL_{iv}	—	—	—	—	—	1.00	(43)[g]
alprazolam	CL_{oral}	—	—	—	1.17	—	—	(44)[h]
	CL_{oral}	—	—	—	0.905	—	—	(45)[h]
aprepitant	CL_{oral}	—	—	1.27	1.72	—	—	(46)
avanafil	CL_{oral}	1.16	0.996	—	—	—	—	NDA 202276[i]
buspirone	CL_{oral}	—	—	0.496	0.376	—	—	(52)[k]
	CL_{oral}	—	0.436	0.623	—	0.707	—	(53)[g]
	CL_{oral}	—	0.465	—	0.377	—	—	(54)[k]
casopitant	CL_{oral}	0.748	0.820	—	—	—	—	(47)
conivaptan	$CL_{iv}\text{-}CL_r$	0.662	1.14	—	—	—	—	(48)[i]
dexamethasone	CL_{iv}	—	—	2.02	1.00	—	—	(55)[g]
eletriptan	CL_{oral}	1.12	1.08	0.727	—	—	—	NDA 021016[g]
eplerenone	CL_{oral}	0.971	0.818	0.676	1.437	—	—	(56)
felodipine	CL_{oral}			0.740[e]				(57)[k]
midazolam	CL_{iv}	—	—	—	—	—	1.69	(49)[g]
	CL_{oral}	—	—	—	1.09	—	—	(12)[l]
oxycodone	-[d]	—	0.625[f]		—	—	—	[m]
tadalafil	CL_{oral}	0.456	0.585	—	—	—	—	(58)[i]
ticagrelor	CL_{oral}	—	—	0.883	—	—	—	(50)[i]
	CL_{oral}	—	—	1.11	—	—	—	NDA 022433[i]
tolvaptan	CL_{oral}	—	0.557	0.529	—	—	—	(51)
triazolam	CL_{oral}	—	—	—	1.57	—	—	(59)[h]
drug B	CL_{oral}	—	—	—	0.731	—	—	—

References after 51 can be found in the Supplementary Text S5 online. Classification of CKD subjects were based on measured urinary creatinine clearance unless otherwise noted. [a]ESRD subjects on dialysis but studied at off-dialysis periods. [b]ESRD subjects not yet receiving dialysis. [c]ESRD subjects and dialysis status not reported. [d]Route of administration in CKD study was not specified. [e]CKD group included subjects with GFR of 7.5 to 77.1. [f]Subjects in moderate to severe CKD subjects were combined in one group. [g]Renal function estimated with creatinine clearance but calculation method not specified. [h]Estimation method of renal function not specified. [i]Renal function estimated with Cockcroft and Gault equation. [j]Unbound fraction data were obtained from summary of original submission file in PMDA website (http://www.info.pmda.go.jp/approvalSrch/PharmacySrchInit). [k]Renal function measured with ^{51}Cr-EDTA clearance. [l]Renal function estimated with the Modification of Diet in Renal Disease (MDRD) Study equation. [m]Data obtained from product labels. —, data not available. AUCR, area under the concentration-time curve ratio; $AUCR_{liver}$, AUCR attributable to the inhibition of hepatic CYP3A4/5; CKD, chronic kidney disease; CL_{iv}, systemic clearance after intravenous administration; $CL_{iv,u}$, systemic unbound clearance after intravenous administration; CL_{oral}, oral clearance; $CL_{oral,u}$, oral unbound clearance; CL_r, renal clearance; CYP, cytochrome P450; DDI, drug-drug interaction; ESRD, end-stage renal disease; F_aF_g, intestinal availability; F_g, fraction not metabolized in gut; f_u, fraction unbound in plasma; NDA, new drug application; PMDA, Pharmaceuticals and Medical Devices Agency, Japan; R_CL_{total}, ratio of clearance calculated with total (bound plus unbound) concentration between CKD and healthy control group; $R\_CL_{unbound}$, ratio of unbound clearance between CKD and healthy control group.

CKD, on average, the estimated R_CL_{CYP} was around one (**Figure 4b,d**), indicating that the change in clearance of CYP3A4/5 model drugs in patients with CKD is modest compared to CYP2D6 model drugs. However, large variability among different drugs makes it difficult to draw robust conclusions. One limitation of this study is that pathways other than CYP2D6,

Table 3 Pharmacokinetic parameters of CYP2D6 and CYP3A4/5 model drugs that have clinical CKD study reports

(a) CYP2D6 model drugs

				DDI or PGx with maximum AUCR		
Drugs	$f_{m,CYP2D6}$	1-$f_{m,CYP2D6}$	$f_{e,urine}$[b]	AUCR	Inhibitors or PGx	References
bufuralol	0.681	0.319	0.0083	3.13	PM vs EM	(33, 60)
encainide	0.966	0.034	0.049	29.0	PM vs EM	(61)
fluoxetine	0.743	0.257	0.012[c]	3.89	PM vs EM	(34, 62)
metoprolol	0.828	0.172	0.15	5.82	PM vs EM	(35, 63)
d-nebivolol	0.970	0.030	0[c]	32.8	PM vs EM	NDA 021742
l-nebivolol	0.982	0.018	0[c]	55.5	PM vs EM	NDA 021742
nortriptyline	0.795	0.205	—	4.88	paroxetine	(64)
paroxetine	0.859	0.141	<0.021	7.11	PM vs EM	(65, 66)[i]
propafenone	0.874	0.126	0.012	7.92	PM vs EM	(67)[i]
risperidone	0.759	0.241	0.030	4.15	fluoxetine	(68, 69)[j]
trimipramine	0.869	0.131	—	7.61	PM vs EM	(70)
venlafaxine	0.830	0.170	0.013	5.88	quinidine	(71, 72)
drug A	≥0.667	<0.333	—	≥3	—	—

(b) CYP3A4/5 model drugs with AUC_{liver} ≥ 3

				DDI with maximum AUCR			F_aF_g or F_g		
Drugs	$f_{m,CYP3A4/5}$	1-$f_{m,CYP3A4/5}$	$f_{e,urine}$[b]	AUCR	$AUCR_{liver}$	Inhibitors	Value	Method	References
alfentanil	0.948	0.052	<0.01	19.05	19.05[f]	troleandomycin	—	—	(69, 73)
alprazolam	0.735	0.265	0.21	3.98	3.77	ketoconazole	0.948	IV/PO	(74–77)
aprepitant	0.708	0.292	0	4.78	3.43	ketoconazole	0.717	IV/PO	NDA 021549
avanafil	0.798	0.202	0.00006[c]	12.83	4.96	ketoconazole	0.387	Hisaka	NDA 202276
buspirone	0.814	0.186	<0.025	19.15	5.39	itraconazole	0.281	IV/PO	(52, 78)[l]
casopitant	0.882	0.118	<0.001	12.06	8.49	ketoconazole	0.704	IV/PO	(79, 80)
conivaptan	0.811	0.189	0.015	10.82	5.28	ketoconazole	0.488	IV/PO	(48), NDA 21697
dexamethasone	0.691	0.309	0.00023[d]	3.24	3.24[f]	itraconazole	—	—	(81)[i]
eletriptan	0.721	0.279	0.090	5.88	3.58	ketoconazole	0.610	IV/PO	(82), NDA 021016
eplerenone	0.755	0.245	0.024	5.39	4.09	ketoconazole	0.759	IV/PO	(83, 84), NDA 021437[j]
felodipine	0.687	0.313	<0.025	6.34	3.19	itraconazole	0.504	IV/PO	[j]
midazolam	0.888	0.112	0[c]	19.63	8.89	ketoconazole	0.453	IV/PO	(85–88)[j]
oxycodone	0.747	0.253	0.090[e]	3.57	3.95	voriconazole	1.106	IV/PO	(89–92)
tadalafil	0.691	0.309	<0.003[c]	4.12	3.24	ketoconazole	0.787	Hisaka	NDA 021368
ticagrelor	0.696	0.304	0.028	7.32	3.28	ketoconazole	0.449	IV/PO	(93), NDA 022433[j]
tolvaptan	0.715	0.285	<0.018	5.40	3.51	ketoconazole	0.651	IV/PO	(94, 95)[k]
triazolam	0.930	0.070	<0.066	27.12	14.28	itraconazole	0.527	IV/PO	(96–99)
drug B	<0.667	≥0.333	—	—	—	—	—	—	—

(c) CYP3A4/5 model drugs with $AUCR_{liver}$ < 3 or whose F_aF_g and F_g were not calculated due to nonlinearity or insufficient clinical pharmacokinetic data

				DDI with maximum AUCR			F_aF_g or F_g		
Drugs	$f_{m,CYP3A4/5}$	$1\text{-}f_{m,CYP3A4/5}$	$f_{e,urine}$[b]	AUCR	$AUCR_{liver}$	Inhibitors	Value	Method	References
aliskiren	—[a]	—[a]	0.075	6.33	0.18	itraconazole	0.029	IV/PO	(100)[k]
anacetrapib	0.513	0.487	<0.001[c]	4.58	2.05	ketoconazole	0.448	Hisaka	(101, 102)
atorvastatin	0.165	0.835	<0.1	4.43	1.20	mibefradil[h]	0.270	IV/PO	(103, 104), NDA 020702
bosentan	—	—	<0.03[c]	3.73	—[g]	clarithromycin	—[g]	—	[j]
colchicine	0.400	0.600	0.27	3.39	1.67	clarithromycin	0.491	IV/PO	(105—107)[l]
ebastine	0.917	0.083	0.001[c]	42.50	—	ketoconazole	—	—	(108)[i]
erythromycin	0.297	0.703	0.12	3.69	1.42	troleandomycin	0.386	IV/PO	(69, 109—111)
loratadine	0.312	0.688	0[c]	4.46	—	ketoconazole	—	—	(108)[i]
maraviroc	0.504	0.496	0.23	5.00	2.01	ketoconazole	0.403	IV/PO	(112, 113)
mirodenafil	0.449	0.551	—	4.89	—	ketoconazole	—	—	(114)
nisoldipine	0.647	0.353	0[c]	25.28	2.83	ketoconazole	0.112	IV/PO	(115—117)[l]
quetiapine	0.665	0.335	<0.01[c]	6.20	—	ketoconazole	—	—	(118, 119)
ranolazine	—	—	<0.05[c]	3.64	—[g]	ketoconazole	—[g]	—	[j]
saxagliptin	0.570	0.430	0.24[c]	3.67	2.33	ketoconazole	0.635	Hisaka	NDA 022350
silodosin	0.154	0.846	0.069	3.09	1.18	ketoconazole	0.383	IV/PO	NDA 022206
simeprevir	—	—	<0.01[c]	6.54	—[g]	erythromycin	—[g]	—	[j]
voclosporin	0.620	0.380	0.0025[c]	18.14	2.63	ketoconazole	0.145	Hisaka	(120, 121)
drug C	<0.667	≥0.333	—	—	—	—	—	—	—
drug D	<0.667	≥0.333	—	—	—	—	—	—	—
drug E	<0.667	≥0.333	—	—	—	—	—	—	—

References after 51 can be found in the Supplementary Text S5 online. [a]Not calculated because $AUCR_{liver}$ was less than one. [b]$f_{e,urine}$ after intravenous administration or $f_{e,urine}$ after oral administration divided by absolute bioavailability, if not indicated otherwise. [c]$f_{e,urine}$ after oral administration. [d]$f_{e,urine}$ after nasal administration. [e]$f_{e,urine}$ after intramuscular administration. [f]AUC = $AUCR_{liver}$ because clinical DDI study was conducted after the intravenous administration of victim drugs. [g]Not calculated because of nonlinearity. [h]DDI reports with cyclosporine A and clarithromycin were not used as these are known inhibitor of OATPs-mediated hepatic uptake. [i]Data obtained from interview forms from PMDA. [j]Data obtained from product labels. [k]Data obtained from summary of original submission file in PMDA website (http://www.info.pmda.go.jp/approvalSrch/PharmacySrchInit). [l]R_B predicted using GastroPlus software. —, data not available. AUCR, area under the concentration-time curve ratio; $AUCR_{liver}$, AUCR attributable to the inhibition of hepatic CYP3A4/5; CKD, chronic kidney disease; CYP, cytochrome P450; DDI, drug-drug interaction; EM, extensive metabolizer; $f_{e,urine}$, fraction eliminated into urine as an unchanged drug; $f_{m,CYP2D6}$, estimated fraction metabolized by CYP2D6; $f_{m,CYP3A4/5}$, estimated fraction metabolized by CYP3A4/5; IV/PO, intravenous/oral method; NDA, new drug application; OATPs, Organic Anion Transporting Polypeptides; PGx, pharmacogenetics; PM, poor metabolizer; PMDA, Pharmaceuticals and Medical Devices Agency, Japan; R_B, blood to plasma concentration ratio.

CYP3A4/5, and renal excretion can contribute to the clearance of model drugs. Another possible source of variability is different effects of CKD on CYP3A4 and CYP3A5.[21] To further evaluate CYP2D6 and CYP3A4/5 activity changes quantitatively, it is imperative to have a good understanding of the detailed elimination mechanisms of each model drug. Nevertheless, our findings are supported by previous data showing that CYP3A4/5 function is not changed in patients with ESRD using a probe substrate, midazolam.[12]

Such observed trends for CYP2D6 and CYP3A4/5 were, however, not consistent with reported results using experimental animals or *in vitro* systems. In experimental animal models of CKD, hepatic activity and expression levels of Cyp2d enzyme were unchanged, while those of Cyp3a family enzymes decreased.[5] Direct inhibition of CYP2D6- and CYP3A4/5-mediated microsomal metabolism was not observed after coincubation with 10% uremic serum or four uremic toxins,[22,23] while coincubation with uremic serum for 4 days decreased CYP3A4 activity in LS 180 cells (unfortunately, they did not examine the coincubation effect on CYP2D6). There are clear needs for further mechanistic studies examining elimination-route dependencies in the effect of CKD on nonrenal eliminations, and we hope that the *in vivo* observation in the current study will stimulate such efforts.

Despite its importance, alteration in the degree of plasma protein binding with CKD is not routinely evaluated in pharmacokinetic studies. With CKD, there is a possibility that the decrease in intrinsic activities of metabolic enzymes or transporters was masked by an increase in plasma unbound fraction, so that clearance measured by total drug concentrations was unaltered or even increased. In such cases, unbound drug concentration can be increased with a modest change in total drug concentration, as seen with drug A (**Table 1**). It is also important to note that the

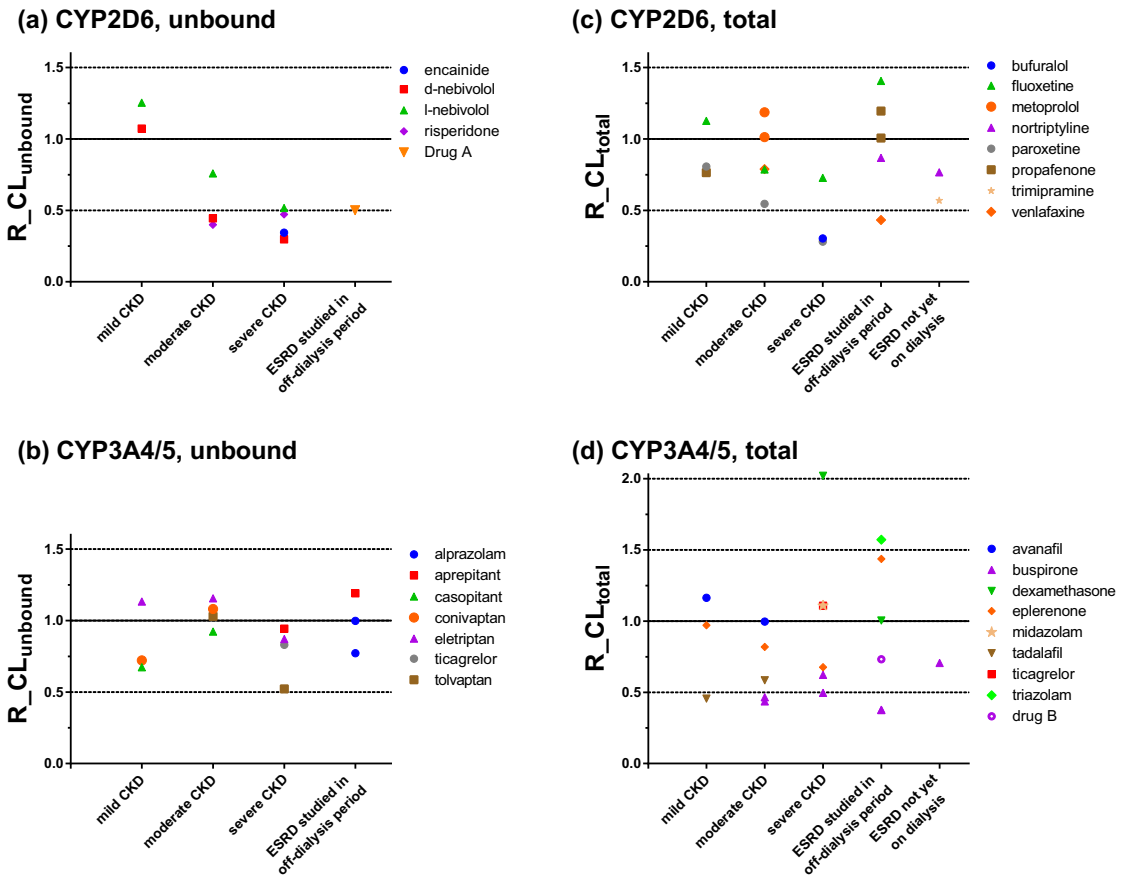

Figure 2 Effect of CKD on (**a,c**) CYP2D6 and (**b,d**) CYP3A4/5 model drugs. Symbols represent (**a,b**) $R\_CL_{unbound}$ in each CKD group of a clinical CKD study for drugs with unbound fraction information in healthy control and CKD groups, or (**c,d**) R_CL_{total} for drugs without unbound fraction information in CKD studies. CKD, chronic kidney disease; CYP, cytochrome P450; ESRD, endstage renal disease; $R\_CL_{unbound}$, ratio of clearance between CKD groups and the healthy control group; $R\_CL_{unbound}$, ratio of unbound clearance between CKD groups and the healthy control group; R_CL_{total}, ratio of clearance calculated with total (bound plus unbound) concentration between CKD groups and the healthy control group.

effects of CKD on protein binding are drug-dependent.[14,24,25] Although we established a comprehensive CKD study dataset, only 5 and 12 model drugs for CYP2D6 and CYP3A4/5, respectively, had sufficient unbound fraction information. In addition, possible protein binding changes in CKD may have biased our evaluation for model drugs that did not have data on unbound concentration. In future studies it is essential to evaluate changes in protein binding in CKD for each drug.

One objective of this study was to compare the degree of change with ESRD patients not yet on dialysis to other CKD groups. The 2012 draft guidance by the FDA suggested that this group may represent the "worst-case" increase in drug exposure and be appropriate for inclusion in a reduced pharmacokinetic design study.[3] However, recruiting ESRD patients not yet on dialysis is difficult, since most ESRD patients are "very likely to be on a dialysis based on the typical standard of care."[26] Alternative groups have been proposed in lieu of ESRD patients not yet on dialysis.[27] Because of the scarcity of data, it is difficult to assess whether ESRD patients not yet on dialysis are better than the severe CKD group to estimate the change in maximum drug exposure; most of the available data for ESRD patients were from those undergoing regular dialysis but studied during an off-dialysis period. Further study is needed to determine whether the inclusion of such patients is beneficial in assessing the effect of CKD on nonrenal elimination pathways.

Despite limitations summarized in **Supplementary Material S4**, the results from our study are useful in predicting pharmacokinetic alterations in CKD patients. In the current study we only focused on two nonrenal elimination pathways, CYP2D6 and CYP3A. Other elimination pathways such as other metabolic enzymes or transporters should be examined to gain comprehensive understanding of the effect of CKD on different nonrenal elimination pathways. One of the potential applications of such examinations is to incorporate observed activity changes of each enzyme or transporter in physiologically based pharmacokinetic (PBPK) models to provide quantitative prediction of CKD effects. While such approaches have been used in recent years,[14,15,28] these system parameters must be made more robust with additional data to improve reliability. To systematically understand the effect of CKD on all nonrenal elimination pathways, and to improve the prediction capability of pharmacokinetic changes with PBPK models using validated

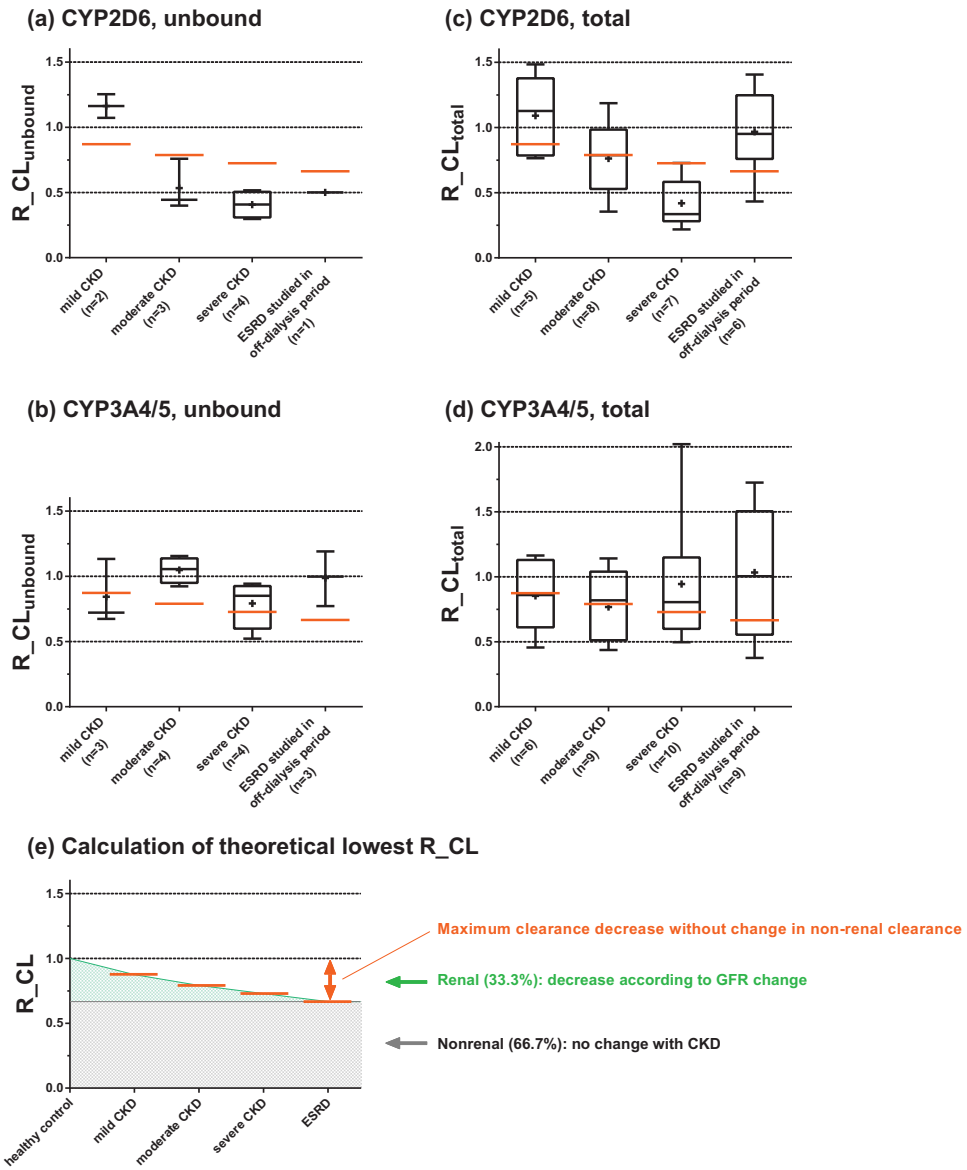

Figure 3 Comparison of observed R_CL and theoretical lowest R_CL without changes in nonrenal clearance for (**a,c**) CYP2D6 and (**b,d**) CYP3A4/5 model drugs, and (**e**) graphical representation of the calculation method of theoretical lowest R_CL. The black box and whisker represent interquartile range of (**a,b**) $R\_CL_{unbound}$ for drugs with unbound fraction information, or (**c,d**) R_CL_{total} for all drugs with CKD studies. "+" symbol represents mean value of R_CL, and the orange lines represent the theoretical lowest R_CL assuming no changes in nonrenal clearance (as shown in (**e**); the values are 0.88, 0.79, 0.73, and 0.69 for the mild, moderate, severe, and the ESRD groups, respectively). CKD, chronic kidney disease; CYP, cytochrome P450; ESRD, endstage renal disease; n, number of CKD studies in each category; $R\_CL_{unbound}$, ratio of clearance between CKD groups and the healthy control group; $R\_CL_{unbound}$, ratio of unbound clearance between CKD groups and the healthy control group; R_CL_{total}, ratio of clearance calculated with total (bound plus unbound) concentration between CKD groups and the healthy control group.

system parameters, cocktail studies in CKD subjects with probe substrates of individual elimination pathways may help compare CKD effect on different pathways.

In summary, this study demonstrated that, although with limited data, the degree of reduction in the clearance with CKD was consistent among multiple CYP2D6 model drugs, and was greater than the estimated decrease assuming no changes in nonrenal clearance. The findings, again based on our limited data, also suggest that the severe CKD group may represent an appropriate "worst-case scenario" to inform the greatest exposure change in CKD for drugs mainly eliminated by CYP2D6. On the other hand, the effect of CKD on CYP3A4/5 was highly variable but modest compared to CYP2D6. Further examination of factors that potentially contributed to the observed variability is necessary, such as the contribution of other nonrenal elimination pathways than CYP3A4/5. The collected information will be useful not only to determine the needs for dedicated CKD studies for new drugs, but also to inform the need and design of future mechanistic studies to understand the effect of CKD on drug disposition.

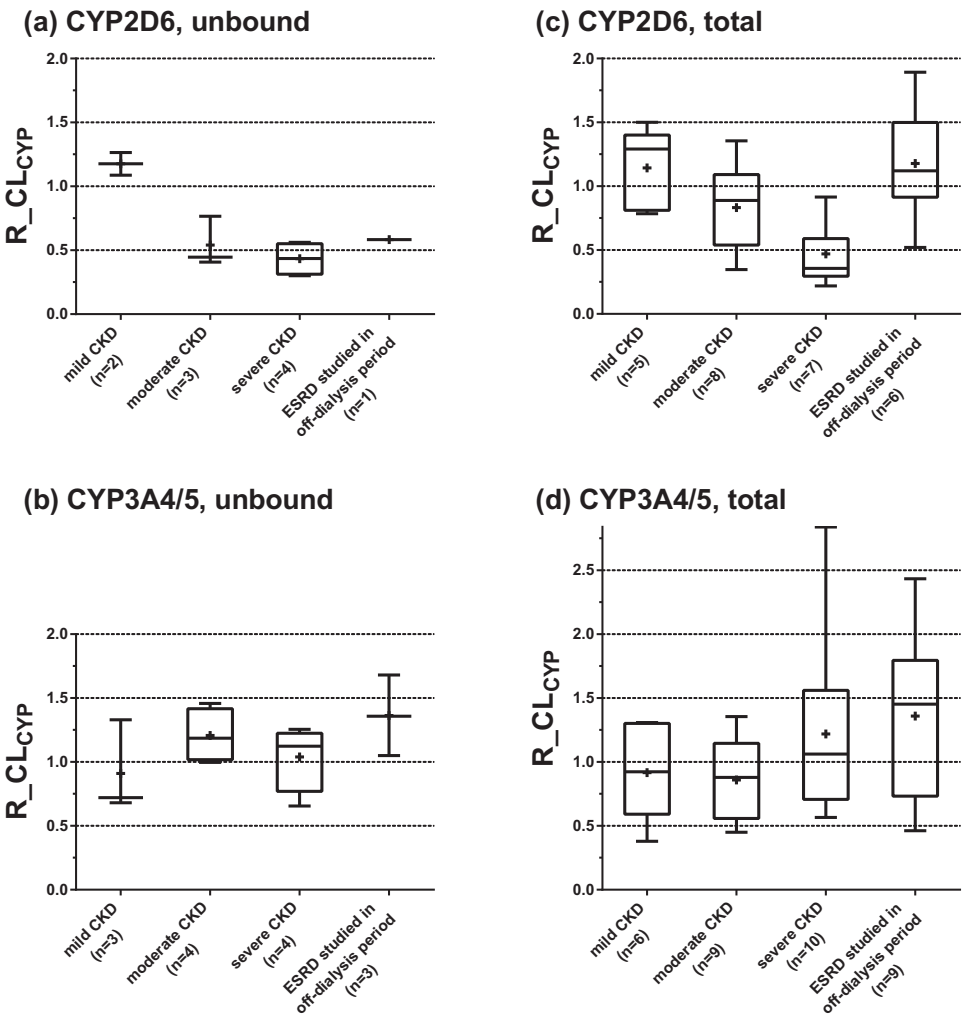

Figure 4 Effect of CKD on (**a,c**) CYP2D6 and (**b,d**) CYP3A4/5 mediated clearance. The black box and whisker represent interquartile range of (**a,b**) unbound R_CL_{CYP} for drugs with unbound fraction information, or (**b,d**) R_CL_{CYP} calculated with total (bound plus unbound) concentration for all drugs with CKD studies. "+" symbol represents mean value of R_CL. CKD, chronic kidney disease; CYP, cytochrome P450; ESRD, endstage renal disease; R_CL_{CYP}, ratio of clearance mediated by CYP2D6 or CYP3A4/5 between CKD groups and the healthy control group.

METHODS

Selection of CYP2D6 and CYP3A4/5 model drugs

The University of Washington Metabolism and Transport Drug Interaction Database (DIDB) and the FDA's new drug application (NDA) reviews (Drugs@FDA) were searched (**Figure 1**) in order to identify a comprehensive list of potential model drugs for individual elimination pathways. For our purposes, a model drug was defined as one that is predominantly cleared by a specific CYP isozyme *in vivo* based on experimentally derived area under the concentration–time curve ratio (AUCR) from DDI or pharmacogenetics studies as described below. The DIDB was first curated for *in vitro* or *in vivo* substrates of major CYP enzymes (CYP1A2, CYP2B6, CYP2C19, CYP2C8, CYP2C9, CYP2D6, CYP2E1, and CYP3A4/5). To include newly developed drugs that were not incorporated in the DIDB at the time of data curation (17 Dec., 2014), NDA reviews of recently approved small molecule drugs (approved between 2014 and July 2015) were also surveyed. In total, 937 drugs were collected as potential model drugs.

For each of 937 drugs, available DDI studies with typical inhibitors for a specific pathway as defined below and CYP2D6 pharmacogenetic studies were examined. Typical inhibitors used in this study were fluoxetine, paroxetine, quinidine, and terbinafine for CYP2D6, and clarithromycin, cyclosporine, erythromycin, fluconazole, itraconazole, ketoconazole, posaconazole, troleandomycin, and voriconazole for CYP3A4/5. If a drug showed a predefined criterion of AUCR of $\geq$3 between the presence and absence of one of typical inhibitors, the drug was identified as a model drug for the respective pathways. Similarly, if a drug showed AUCR of $\geq$3 between poor or intermediate vs. extensive metabolizers of CYP2D6, the drug was identified as a CYP2D6 model drug. The criterion of AUCR $\geq$3 was selected to enrich the list of drugs with those having a high contribution ($\geq$66.7%) of CYP2D6 or CYP3A4/5 in their elimination.

Because some of the DDIs may be caused by the inhibition of other CYP enzymes or transporters due to overlapping substrate specificity, drugs with such DDI cases were manually excluded from the list of model drugs by consensus of two or more authors. Also, two HIV protease inhibitors were excluded because they are usually given with ritonavir, a strong CYP3A4/5 inhibitor. One of the 33 potential CYP2D6 model drugs and 14 of 87 potential CYP3A4/5 model drugs were excluded for these reasons (**Supplementary Table S1**).

Collection of clinical CKD studies for model drugs

PubMed, the DIDB, NDA review documents by the FDA or Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, and original study reports submitted to the FDA were queried for the availability of

dedicated clinical CKD studies for the 32 and 73 model drugs for CYP2D6 and CYP3A4/5, respectively. Keywords used for PubMed queries were "[drug name] AND pharmacokinetics" and/or "[drug name] AND renal impairment." The results of population pharmacokinetics-based analysis or studies using historical values as control were excluded. Ratios of clearance values between the CKD groups and the healthy control group were calculated from one of the following parameters in this order of preference: CL_{oral}, nonrenal clearance after intravenous administration ($CL_{iv,NR}$), CL_{iv}. CL_{oral} was preferred over $CL_{iv,NR}$ or CL_{iv}, because changes in hepatic intrinsic clearance for high-clearance drugs cannot be captured in $CL_{iv,NR}$ or CL_{iv}. If available, ratios of clearance based on unbound plasma concentration ($CL_{unbound}$) or ratios of CL_{total} divided by fraction unbound in plasma (f_u) of each CKD group were calculated.

In most of the studies, classification of CKD groups was consistent with those proposed in the FDA guidance on CKD studies,[3] where mild, moderate, severe CKD, and ESRD groups were defined as 60–89, 30–59, 15–29, and <15 (or requiring dialysis) of either estimated glomerular filtration rate (GFR) (ml/min/1.73 m^2) or creatinine clearance (ml/min) as described in **Tables 1**, **2** and **Supplementary Table S2**. If classification in a study was inconsistent, the mean of minimum and maximum values for each group in the study was calculated, and the calculated mean value was used to judge to which group should the observed group be assigned in the summary table of this study (e.g., if a group have GFR values of 20–49, average is 34.5 and the group is classified as a moderate CKD group [30≤34.5<60]). Values with fewer than three subjects in a CKD group were excluded from the analysis (predefined criteria). For CYP2D6 model drugs, CYP2D6 activities (either by genotyping or phenotyping) were also captured from study reports.

Estimation of the contribution of hepatic CYP3A4/5 inhibition to the overall effect of typical inhibitors on the oral clearance of CYP3A4/5 model drugs

In order to differentiate the contribution of hepatic CYP3A4/5 inhibition to the observed magnitude of clinical DDI for 38 CYP3A4/5 model drugs, we calculated intestinal availability (F_aF_g) or fraction escaping gut-wall elimination (F_g) of these drugs. Then, AUCR attributable to hepatic CYP3A4/5 inhibition was calculated by $AUCR_{liver} = F_gAUCR$ ($\geq F_aF_gAUCR$) as described below.

F_aF_g or F_g values were calculated with one of the following methods (in the order of preference, depending on the data available) for CYP3A4/5 drugs that had clinical CKD reports (**Table 3**)[29]:

1. IV/PO method: $F_aF_g = F / [1-CL_{iv,B} \times (1-f_{e,urine}) / Q_h]$, where $CL_{iv,B}$, $f_{e,urine}$, F, and Q_h represent blood clearance after intravenous administration, fraction eliminated into urine as an unchanged drug, absolute bioavailability, and hepatic blood flow rate, respectively (25.5 ml/min/kg[30]). If the blood-to-plasma concentration ratio was not reported, this value was predicted using GastroPlus v. 9.0 (Simulations Plus, Lancaster, PA).
2. An F_g estimation method proposed by Hisaka *et al.*,[29] which utilizes changes in both AUC and terminal half-life with DDI to differentiate the inhibitor effects on hepatic and intestinal CYP3A4/5.

Two drugs (alfentanil and dexamethasone) having both clinical DDI and CKD studies conducted only after intravenous administration and three drugs (bosentan, ranolazine, and simeprevir) exhibiting nonlinear pharmacokinetics at therapeutic doses were excluded. Among the remaining 33 drugs, F_aF_g values of 22 drugs were estimated either by the intravenous/oral (IV/PO) method. Because of the instability in estimating F_g with Method 2 for high clearance drugs, we estimated F_g value only for 5 out of remaining 11 drugs with the method of Hisaka *et al.*,[29] for which observed oral clearance was lower than hepatic blood flow rate. In total, F_aF_g or F_g were calculated for 29 drugs.

AUCR attributable to intestinal CYP3A4/5 inhibition can be estimated as $1/F_g$ ($\leq 1/F_aF_g$) under the assumption that typical CYP3A4/5 inhibitors completely block intestinal CYP3A4/5 function. $AUCR_{liver}$ was therefore estimated with F_gAUCR ($\geq F_aF_gAUCR$), where AUCR represented the AUC ratio in the presence and absence of a typical CYP3A4/5 inhibitor. As a result, 11 of 29 drugs were found to have less than threefold of AUCR attributable to the inhibition of hepatic CYP3A4/5 ($AUCR_{liver}$), suggesting less than 66.7% contribution of CYP3A4/5 in the systemic elimination (**Table 3**). These 11 drugs were excluded from further analysis.

Quantitative interpretations of the observed ratios of clearance

First, theoretical lowest values in ratios of clearance without changes in nonrenal clearance were calculated (**Figure 3e**) to be compared with observed ratios of clearance (R_CL_{obs}). In this calculation, we assumed that at most 33.3% of systemic elimination was mediated by the renal pathway, because the model compounds showing AUCR of ≥3 should have ≥66.7% contribution of the hepatic pathway of interest. It was also assumed that a decrease in renal clearance was parallel to the decrease in GFR with different degrees of CKD, regardless of the contribution of active tubular secretion or reabsorption, based on a reported meta-analysis of the CKD effect on renally eliminated drugs.[15]

Second, changes in CYP2D6 and CYP3A4/5 pathways were calculated by the following equations, using individually estimated contribution of the pathway of interest:

$$f_{m,CYP2D6} = 1 - \frac{1}{AUCR}$$

$$f_{m,CYP3A} = 1 - \frac{1}{AUCR_{liver}}$$

$$R\_CL_{obs} = R\_CL_{CYP} \times f_{m,CYP} + R\_CL_r \times (1 - f_{m,CYP})$$

$$\Longleftrightarrow R\_CL_{CYP} = \frac{R\_CL_{obs} - R\_CL_r \times (1 - f_{m,CYP})}{f_{m,CYP}}$$

where R_CL_r represents the ratio of renal clearance in each CKD group as described below. The assumptions used to derive these equations were that 1) all elimination pathways other than CYP2D6 or CYP3A4/5 decrease in parallel with GFR, and 2) CKD does not affect the absorption of model drugs. To compare with ($1-f_{m,CYP}$), $f_{e,urine}$ values were also calculated, either as $f_{e,urine}$ after intravenous administration or $f_{e,urine}$ after oral administration divided by absolute bioavailability (**Table 3**).

In both calculations, GFR of 120 ml/min and 0 ml/min for healthy control and ESRD groups, and average of maximum and minimum values for each CKD group (74.5, 44.5, 22.5 for mild, moderate, severe CKD, respectively) were used to calculate R_CL_r of 0.625, 0.375, 0.188, 0 for mild, moderate, severe CKD, and ESRD, respectively.

Additional Supporting Information may be found in the online version of this article.

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CONFLICT OF INTEREST/DISCLOSURE

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AUTHOR CONTRIBUTIONS

K.Y., B.S., L.Z., P.Z., D.R.A., T.D.N., A.R.-H., I.Z., and S.M.-H. wrote the article; K.Y., L.Z., P.Z., A.R.-H., and S.M.-H. designed the research; K.Y. and B.S. performed the research; K.Y., B.S., L.Z., P.Z., D.R.A., T.D.N., A.R.-H., I.Z., and S.M.-H. analyzed the data.

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