Supplemental Data

Application of a Physiologically Based Pharmacokinetic Model Informed by a Top-Down Approach for the Prediction of Pharmacokinetics in Chronic Kidney Disease Patients

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Supplementary Table S1

Summary of *in vitro* and *in vivo* Data for Analysis of Pharmacokinetics in Chronic Kidney Disease

Drug	f_p			V_{ss} (mL/kg)			f_e			CL (mL/min/kg)			Normalized AUC (ng hr/mL)			$t_{1/2}$ (hr)			Analysis of Alteration				Prediction		Ref
	HV	Mod	Sev	HV	Mod	Sev	HV	Mod	Sev	HV	Mod	Sev	HV	Mod	Sev	HV	Mod	Sev	f_p	V_{ss}	CL_R	CL_{UintH}	CL	PK	
Alfuzosin							0.11	0.086	0.015				1870	3041	2831							x			59
Aliskiren							0	0	0				169	544	258							x			83
Alvimopan							0	0	0				291	310	437							x			PP
Argatroban				156	164	200														x					PP
Aripiprazole	0.0154		0.0146				0.0005		0.0018				43755		34624				x			x			57
Asenapine	0.037	0.042	0.043				0	0	0				606	665	680				x			x			67
Azilsartan							0.081	0.038	0.011				45182	64955	75109							x			69
Aztreonam	0.464	0.558	0.536	200	170	190	0.6	0.38	0.24	1.306	0.616	0.426							x	x	x		x		PP
Batanopride*	0.46	0.36	0.35	1476	1791	1445	0.2	0.14	0.05	9.154	8.630	5.756				2.7	3.3	4.8	x	x			x	x	77
Bivalirudin	1						0.341	0.232		3.700	2.500												x		PP
Bosentan							0		0				4211		4211							x			28
Bupropion							0	0					241	573								x			82
Cabergoline							0.012	0.013	0.004				200	264	198							x			PP
Candesartan	0.005		0.008																x						PP
Carumonam*	0.82			184	215	187	0.782	0.546	0.426	1.435	0.594	0.309				2.0	4.3	8.1		x	x		x	x	39
Cefepime*	0.2			152	196	211	0.877	0.776	0.458	1.264	0.464	0.272				2.0	6.0	11.2		x	x		x	x	23
Cefotetan*	0.12			166	165	148	0.494	0.463	0.289	0.595	0.272	0.199				4.3	8.3	10.4		x	x		x	x	72
Cerivastatin	0.0075	0.0083	0.0115				0	0	0				3150000	7396667	5250000				x			x			84
Cidofovir*	0.05			323	371	301	0.86	0.69	0.75	1.819	0.479	0.202				2.5	11.6	20.9		x	x		x	x	11
Cilostazol	0.0347	0.0376	0.0439				0	0	0				9850	8465	5769				x			x			56
Cinacalcet	0.053	0.073	0.069																x						PP
Cinaciguat	0.0045	0.0053	0.0066	224	304	289													x	x					50
Clazosentan	0.02		0.036	344		385													x	x					12
Clobazam	0.11	0.121					0.018	0.021					43824	41983					x			x			PP
Conivaptan	0.0052	0.0053	0.0056				0	0	0				651	1176	1155				x			x			PP
Cyclophosphamide*	0.85			466	564	427	0.191	0.058	0.056	1.587	0.899	0.638				3.2	6.0	7.7		x			x	x	37
Dalfopristin				420		400														x					20
Daptomycin	0.108	0.098	0.124				0.554	0.354	0.223	0.132	0.067	0.058									x		x		PP
Darifenacin	0.02	0.012	0.011				0	0	0				232	532	252				x			x			PP
Desloratadine							0	0	0				582	1232	1335							x			PP
Desmopressin				543	629	543														x					1
Desvenlafaxine							0.336	0.248	0.185				3490	5572	6661							x			65
Dexmedetomidine				1310		1400														x					PP
Dofetilide	0.371	0.321																	x						PP
Doripenem	0.919			201	199	209	0.83	0.703	0.427	2.806	1.028	0.555								x	x		x		PP
Doxazosin							0		0				9583		11508							x			14
Emedastine							0		0				699		1720							x			44
Empagliflozin							0.161	0.077	0.036				4346	5128	6670							x			54

*, PK parameters were recalculated from plsama concentration-time profile; HV, Healthy Volunteer; Mod, Moderate CKD; Sev, Severe CKD; PP, PharmaPendium database

Supplementary Table S1

Continued

Drug	f_p			V_{ss} (mL/kg)			f_e			CL (mL/min/kg)			Normalized AUC (ng hr/mL)			$t_{1/2}$ (hr)			Analysis of Alteration				Prediction		Ref
	HV	Mod	Sev	HV	Mod	Sev	HV	Mod	Sev	HV	Mod	Sev	HV	Mod	Sev	HV	Mod	Sev	f_p	V_{ss}	CL_R	CL_{UintH}	CL	PK	
Enprofylline*	0.55	0.586	0.661	647	480	456	0.822	0.68	0.311	4.196	1.348	0.347				2.0	4.5	15.8	x	x	x		x	x	52
Eplerenone							0.02	0.016	0.009				9881	11423	12740							x			70
Eprosartan	0.014	0.016	0.027				0.0278	0.0218	0.0028				1144	1379	1963				x			x			60
Ertapenem	0.06			114	95	105	0.431	0.383	0.225	0.417	0.191	0.105								x	x		x		PP
Eszopiclone							0.0676	0.0591	0.0492				6525	9616	10488							x			PP
Etoricoxib	0.081		0.126	1771		1886	0	0	0				19536	20248	18293				x	x		x			2
Exemestane							0.001	0.0004	0.0005				86	233	191							x			41
Febuxostat	0.009	0.008	0.012				0.017	0.0125	0.00759				7688	10392	14438				x			x			61
Felbamate							0.291	0.212	0.12				30683	49933	52850							x			34
Felcainide				7300	7700															x					PP
Fenofibrate	0.0083	0.0151	0.0198																x						PP
Fesoterodine	0.54	0.43	0.43				0.07	0.04	0.028				334	612	778				x			x			PP
Fexofenadine							0.1	0.0655	0.0244				1386	2797	3967							x			PP
Fingolimod							0		0				3738		5931							x			PP
Fludarabine	0.75						0.641	0.558	0.359	2.271	1.900	0.957									x		x		PP
Flutamide							0.000098	0.000056	0.00012				25	23	26							x			4
Fluvastatin							0	0	0				595	751	679							x			6
Fondaparinux	0.06			126	114	121	0.66	0.47	0.17	0.111	0.049	0.020								x	x		x		PP
Foscarnet				310	430	570														x					PP
Fosfluconazole	0.042	0.05	0.05	150	150	160	0.018	0.02	0.004	1.280	1.420	1.370							x	x			x		76
Fosinopril				134	127	166														x					40
Gadobenate	1			347	256	221	0.868	0.744	0.692	2.629	0.686	0.357								x	x		x		PP
Gadobutrol	1			200		220	1		0.773	1.386		0.157								x	x		x		PP
Gadofosveset	0.164			160	190	180	0.742	0.691	0.658	0.119	0.069	0.050								x	x		x		PP
Gadoxetate	0.1			279	231		0.484	0.436		1.443	0.994									x	x		x		PP
Grepfloxacin							0.051	0.027	0.015				1628	2759	1938							x			32
Hydromorphone							0	0					221	426								x			31
Iloperidone							0		0				649		805							x			PP
Iomeprol	1			229	223	272	0.935	0.851	0.683	1.848	0.546	0.266								x	x		x		51
Isepamicin*	0.945			91	155	167	1	0.94	0.773	0.501	0.198	0.099				3.1	11.9	29.1		x	x		x	x	36
Itraconazole	0.0025	0.0027	0.0031	9486	12857	12314													x	x					PP
Ketoprofen	0.0057	0.0075	0.0086				0	0	0				12133	17733	25200				x			x			PP
Lamotrigine							0.0811		0.054				33110		36085							x			87
Lenalidomide	0.598	0.628	0.602																x						19
Letrozole							0	0	0				36512	49756	26600							x			PP
Lidocaine*	0.3			1723	1736	1521	0	0	0	11.37	8.763	5.070				2.3	3.1	4.4		x			x	x	25
Linagliptin							0.232	0.368	0.308				793	1231	989							x			35
Linezolid				693	613	633	0.311	0.285	0.098				13750	16000	16510					x		x			10, 53

*, PK parameters were recalculated from plsama concentration-time profile; HV, Healthy Volunteer; Mod, Moderate CKD; Sev, Severe CKD; PP, PharmaPendium database

Supplementary Table S1

Continued

Drug	f_p			V_{ss} (mL/kg)			f_e			CL (mL/min/kg)			Normalized AUC (ng hr/mL)			$t_{1/2}$ (hr)			Analysis of Alteration				Prediction		Ref
	HV	Mod	Sev	HV	Mod	Sev	HV	Mod	Sev	HV	Mod	Sev	HV	Mod	Sev	HV	Mod	Sev	f_p	V_{ss}	CL_R	CL_{UintH}	CL	PK	
Losartan							0.0325	0.0133	0.0027				776	849	1232							x			PP
Maribavir	0.0011	0.0012	0.0015																x						78
Meloxicam	0.00545	0.00661	0.00926																x						PP
Memantine	0.592	0.588	0.682				0.337	0.236	0.162				5682	10912	13467				x			x			62
Meperidine	0.418	0.555		3990	3850		0.069	0.127		4.854	1.849								x	x			x		16
Meropenem*	0.98			165	182	193	0.77	0.53	0.38	2.671	1.048	0.684				0.9	2.4	4.4		x	x		x	x	21
Metoclopramide							0.219	0.204	0.113	8.020	3.670	3.590											x		49
Metoprolol	0.88			3200		3500	0.145		0.03	11.43		13.28	1827		2267					x			x		43
Metrifonate							0.019	0.011	0.006				2418	2633	2746							x			27
Micafungin	0.0021		0.0024	190		202	0		0	0.163		0.180							x	x			x		PP
Mirabegron	0.32	0.27	0.27																x						26
Mirodenafil	0.0064		0.0066				0		0				466		550				x			x			66
Mivacurium				287	232	276														x					PP
Mycophenolate							0	0	0				3150	3703	5502							x			PP
Nebivolol	0.0179	0.0211	0.0202																x						PP
Nicardipine	0.05						0	0		10.42	6.533												x		3
Nifedipine	0.04	0.053	0.065	780	1360	1470													x	x					45
Nisoldipine							0	0	0				89	126	112							x			PP
Oseltamivir							0.051	0.02	0.007				141	195	152							x			PP
Oxymorphone							0	0	0				66	98	114							x			PP
Paliperidone	0.301	0.25	0.268																x						PP
Palonosetron	0.38			8814		9543	0.303		0.156	2.471		2.129								x			x		PP
Pantoprazole							0		0				6650		9275							x			PP
Paracetamol							0	0	0				4250	4450	3855							x			17
Paricalcitol	0.0006	0.0006	0.0007																x						PP
Paroxetine							0	0	0				1339	2457	4774							x			30
Pemetrexed	0.18	0.207	0.266	232	238	314													x	x					PP
Piroxicam	0.0142	0.0148					0	0					461132	419664					x			x			71
Pitavastatin	0.00414	0.00405					0	0					2187	3925					x			x			PP
Prucalopride	0.68	0.69	0.72																x						73
Quetiapine							0		0				1171		1747							x			79
Quinupristin				270		230														x					20
Raloxifene							0	0					14	21								x			24
Ramelteon							0	0	0				27	37	45							x			PP
Ranitidine	0.85			847	473	523	0.786	0.477	0.29	10.61	4.343	3.000								x	x		x		46
Ranolazine							0	0	0				847	1446	1685							x			42
Rasagiline							0	0					298	236								x			PP
Reboxetine	0.0293	0.0478	0.0485				0.083	0.0737	0.0344				36855	78085	103653				x			x			22

*, PK parameters were recalculated from plsama concentration-time profile; HV, Healthy Volunteer; Mod, Moderate CKD; Sev, Severe CKD; PP, PharmaPendium database

Supplementary Table 1

Continued

Drug	f_p			V_{ss} (mL/kg)			f_e			CL (mL/min/kg)			Normalized AUC (ng hr/mL)			$t_{1/2}$ (hr)			Analysis of Alteration				Prediction		Ref
	HV	Mod	Sev	HV	Mod	Sev	HV	Mod	Sev	HV	Mod	Sev	HV	Mod	Sev	HV	Mod	Sev	f_p	V_{ss}	CL_R	CL_{UintH}	CL	PK	
Regadenoson	0.674	0.719	0.691	1064	956	906	0.65	0.36	0.16	8.329	4.757	3.571							x	x	x		x		PP
Repaglinide							0	0	0				1046	1511	2720							x			58
Risperidone	0.159	0.141	0.162				0.048	0.096	0.033				1833	5396	3791				x			x			75
Rivaroxaban	0.073	0.082	0.076				0.292	0.131	0.104				9041	14993	16153				x			x			48
Rizatriptan							0.13	0.055	0.025				459	613	615							x			PP
Ropivacaine	0.0359	0.0354	0.0327	890	790	812	0.0053	0.0087	0.0104	6.030	5.247	4.985							x	x			x		68
Rosiglitazone	0.0016	0.0015	0.0022				0	0	0				26713	29286	21984				x			x			18
Saxagliptin							0.2	0.12	0.07				1705	2403	3442							x			8
Sildenafil	0.027	0.02	0.022				0	0	0				1058	1235	2127				x			x			64
Silodosin	0.031	0.021																	x						PP
Sisomicin				174	169	185														x					63
Sparfloxacin							0.083	0.092	0.04				4049	8610	7018							x			29
Sulpiride	1			859	1070	939	0.764	0.463	0.340	1.945	1.447	0.741								x	x		x		9
Tadalafil							0	0					20076	34377								x			33
Tamsulosin	0.011	0.009	0.011																x						PP
Tapentadol							0.0233	0.0171	0.00651				263	309	310							x			PP
Telaprevir							0		0				1575		1742							x			PP
Telavancin	0.135	0.122	0.133				0.402	0.318	0.254	0.228	0.185	0.103									x		x		PP
Temocapril							0.017	0.003	0.001				460	765	600							x			74
Teriflunomide	0.0025		0.0025																x						PP
Theophylline	0.6			480		430	0		0	0.766		0.782								x			x		47
Tiagabine	0.041	0.0429	0.0534				0	0	0				9279	8045	9255				x			x			15
Ticagrelor	0.0016		0.0021																x						13
Tigecycline	0.2			10526		8648	0.212		0.06	5.801		4.432								x			x		PP
Tiotropium	0.25	0.26	0.26	35333	17318	24219	0.601	0.399	0.374	10.86	4.187	3.635							x	x	x		x		81
Tirofiban	0.35			507	457	399	0.447	0.278	0.112	7.329	2.886	1.471								x	x		x		PP
Tomopenem*	0.911			222	234	173	0.574	0.626	0.412	1.633	0.553	0.267				2.2	8.2	8.2		x	x		x	x	55
Vandetanib	0.058	0.060	0.065																x						85
Vardenafil	0.0782	0.0683	0.0903				0.0101	0.00553	0.00415				273700	357000	330050				x			x			PP
Varenicline	0.879	0.853	0.892																x						PP
Vilazodone	0.79	0.745					0.00814	0.0058					3463	3836					x			x			7
Vildagliptin							0.188	0.134	0.066				1669	2856	3115							x			38
Zafirlukast							0		0				3505		5287							x			PP
Zanamivir*	0.1			201	204	217	0.897	0.74	0.613	1.091	0.410	0.247				2.7	6.4	11.6		x	x		x	x	86
Zibotentan	0.228	0.266	0.279																x						80
Zileuton	0.063	0.075	0.083				0	0	0				2068	2897	2457				x			x			5
Ziprasidone	0.0012	0.0016	0.0013																x						PP

*, PK parameters were recalculated from plsama concentration-time profile; HV, Healthy Volunteer; Mod, Moderate CKD; Sev, Severe CKD; PP, PharmaPendium database

Supplementary Table S2

Summary of 1st and 2nd Dataset

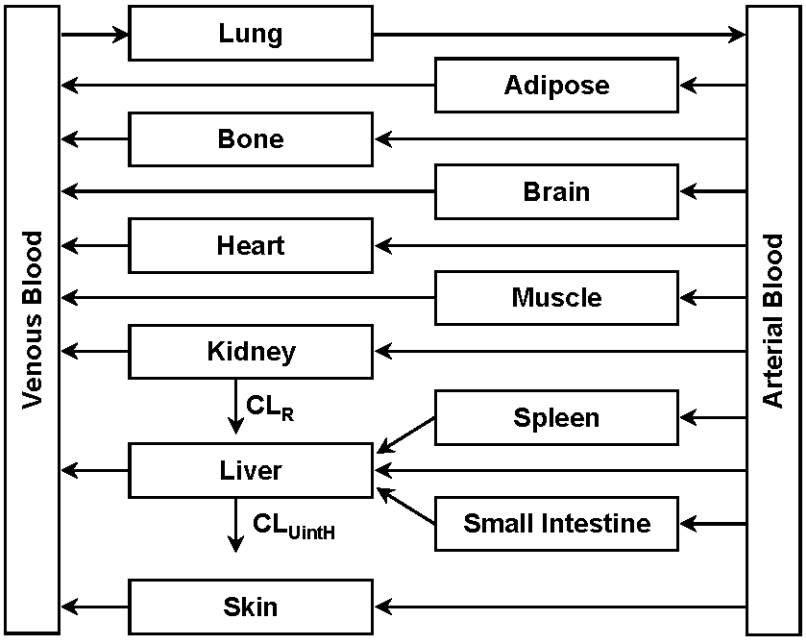
Dataset	N	Administration	Route of Elimination	f_e		Number of Compound in Each Group
				Mean	Range	
1st	76	PO	Non-renal	0.05	0 – 0.34	Basic: 42 Acidic: 15 Neutral: 19
2nd	40	IV	Renal Non-renal	0.50	0 – 1	Basic: 15 Acidic: 16 Neutral: 6 Unknown: 3

The 1st dataset was used to obtain SF for CL_{UintH} from the alteration in disease conditions.
The 2nd dataset was used to validate the predictability of SF for CL_{UintH}.

Supplementary Table S3

Summary of Physiological Parameters used in the PBPK Model

Tissue	Tissue Volume (mL/kg)	Blood Flow (mL/min/kg)
Venous blood	51.4	--
Arterial blood	25.7	--
Lung	7.6	68.3
Adipose	233.8	3.7
Bone	105.1	3.7
Brain	20	8.9
Heart	4.7	3.0
Muscle	400	12.6
Kidney	4.4	14.1
Liver	25.7	4.5
Spleen	2.6	1.1
Small intestine	17.1	13
Skin	37.1	3.7



Supplementary Fig. S1

Scheme of PBPK model used for simulation of plasma concentration-time profiles in HV and CKD patients.

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