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Supplementary Materials: A Whole-Body Physiologically Based Pharmacokinetic Model Characterizing Interplay of OCTs and MATEs in Intestine, Liver and Kidney to Predict Drug-Drug Interactions of Metformin with Perpetrators

Yiting Yang, Zexin Zhang, Ping Li, Weimin Kong, Xiaodong Liu and Li Liu

1. Physiological parameters for human used in the PBPK model.

Table S1. Physiological parameters for human used in the PBPK model.

Tissue	V (mL) [1,2]	Q (mL/min) [1]	Transit rate constant (min^{-1}) [3,4]	pH [5]
Lung	1170	5600	/	
Kidneys	280	1240	/	
Heart	310	240	/	
Liver	1690	300	/	
Muscle	35,000	750	/	
Skin	7800	300	/	
Brain	1450	700	/	
Adipose	10,000	260	/	
Rob	5100	592	/	
Spleen	190	80	/	
Artery	1730	5600	/	
Venous	3470	5600	/	
Stomach	160	38	0.0462	
Duodenum	70	118	0.0462	5.67
Jejunum	209	413	0.012	6.51
Ileum	139	244	0.0058	7.42
Cecum	116	44	0.004	NA
Colon	1116	281	0.0013	6.47

2. Ratios of concentration in tissue to plasma for building PBPK model.

Table S2. Ratios of concentration in tissue to plasma for metformin (Met), cimetidine (Cim), pyrimethamine (Pyr), trimethoprim (Tri), ondansetron (Ond), rabeprazole (Rab) and verapamil (Ver) [6].

Tissue	Met	Cim	Pyr	Tri	Ond	Rab	Ver
pKa	11.8	6.9	7.77	7.16	7.34	5	8.5
LogP	−1.43	0.48	2.62	1.28	2.56	2.3	3.79
Adipose	0.18	1.89	6.8	3.8	39.02	0.08	12.95
Liver	1.6	1.46	7.5	1.9	1.17	0.10	60.55
Muscle	1.7	1.18	1.23	0.98	0.74	0.08	7.58
Lung	1.46	2.35	2.4	2.04	1.48	0.22	14.24
Kidney	1.49	1.58	6.8	1.9	1.12	0.14	54.70
Brain	1.72	1.62	1.9	1.53	1.99	0.06	8.69
Heart	1.47	1.42	2.7	1.34	1.06	0.17	19.27
Intestine	1.5	1.18	3.1	1.3	2.17	0.17	21.87
Skin	1.11	2.31	2.1	1.94	3.12	0.29	12.49

Spleen	1.66	2.02	3.6	1.89	0.73	0.11	25.06
Stomach	1.5	1.18	3.1	1.3	0.74	0.08	21.87
Rest	1.2	0.01	0.01	1	0.01	0.01	0.01

3. The investigation of saturable metformin absorption

Table S3 and S4 are the observed and predicted pharmacokinetic parameters of metformin for different dosage, respectively. Simulation demonstrated that non-linear pharmacokinetics of metformin was attributed to transporter-mediated intestinal absorption.

Table S3. The observed pharmacokinetic parameters of metformin for different dosage.

Dose (mg)	Ref.	C_{max} (ug/mL)	AUC (h·ug/mL)	Dose/AUC
250	[7]	0.59	4.26	58.7
250	[8]	0.78	4.98	50.2
250	[9]	0.74	4.89	51.1
500	[10]	1.1	5.8	86.2
500	[11]	1.55	9.08	55.1
500	[12]	1.19	6.58	76.0
500	[13]	1.21	7.40	67.6
500	[14]	0.77	5.96	83.9
500	[15]	1.3	6.8	73.5
500	[16]	2.1	16.9	29.6
500	[17]	1.14	6.5	76.9
500	[18]	1.05	6.3	79.4
500	[19]	2.0	12.1	41.32
500	[20]	0.84	6.3	79.4
500	[21]	0.99	6.55	76.3
750	[22]	1.46	6.52	115.0
750	[23]	1.51	8.22	103.9
750	[24]	1.5	9.4	79.8
750	[25]	4.2	24.69	30.4
750	[26]	1.38	9.17	81.8
850	[27]	1.3	7.7	110.4
850	[28]	1.2	7.2	118.1
850	[29]	1.81	11.4	74.6
850	[30]	1.17	6.69	127.1
850	[31]	2.28	15.2	55.9
850	[32]	1.26	14.2	59.9
1000	[33]	2.0	13.2	75.8
1000	[34]	1.8	11.1	90.1
1000	[35]	2.06	12.41	80.58
1000	[36]	1.35	10.3	97.1
1000	[37]	2.35	12.81	78.1
1000	[38]	2.19	14	71.4
1000	[39]	1.79	12.57	79.5
1000	[40]	1.18	7.95	125.8
1000	[41]	1.46	10.6	94.3

Table S4. The predicted pharmacokinetic parameters of metformin for different dosage.

Dose (mg)	C_{max} (ug/mL)	AUC (h·ug/mL)	Dose/AUC
250	0.67	4.80	52.06
500	0.95	7.68	65.11
750	1.22	10.19	73.61
850	1.32	11.15	76.26
1000	1.47	12.55	79.68

4. Quantitatively predicted disposition kinetics for perpetrators

Table S5. The observed pharmacokinetic parameters of perpetrators in different references.

Drug	Ref.	Dose (mg)	C_{max} (μg/mL)		AUC_{0-t} (μg·h/mL)	
			Pre	Obs	Pre	Obs
Cimetidine	[42]	400	2.06	2.20	9.17	8.03
	[43]	300	1.53	1.53	6.68	5.22
	[44]	400	2.06	1.5	8.90	10.4
	[45]	400	2.06	1.93	8.61	8.4
	[45]	800	4.11	3.7	17.28	17.89
	[46]	800	4.11	2.47	16.76	11.49
Pyrimethamine	[47]	50	0.5	0.76	47.66	76
	[48]	75	0.86	0.86	51.78	124.6
	[49]	75	0.86	0.38	106.42	79.42
Trimethoprim	[50]	210	2.18	2.35	28.26	37.1
	[51]	1400	13.76	12.78	302.34	299.31
Ondansetron	[52]	8	0.046	0.0272	0.203	0.198
	[53]	8	0.046	0.037	0.233	0.254
	[54]	8	0.046	0.033	0.253*	0.287*
Rabeprazole	[55]	40	0.40	0.502	1.26	1.315
	[55]	40	0.40	0.444	1.26	1.332
	[56]	20	0.20	0.252	0.62	0.575
	[57]	10	0.10	0.15	0.29	0.36
	[58]	20	0.20	0.47	0.62	0.90
	[56]	20	0.20	0.25	0.62	0.58
Verapamil	[59]	40	0.050	0.033	0.28	0.22
	[60]	80	0.099	0.13	0.564	0.387
	[61]	80	0.099	0.082	0.439	0.17
	[62]	160	0.20	0.16	0.82	0.80

* AUC is calculated from 0 to ∞.

5. The administration dosage for coadministration of metformin and perpetrators

The administration dosage of metformin and 6 perpetrators, cimetidine, pyrimethamine, trimethoprim, ondansetron, rabeprazole and verapamil were shown in Table S6.

Table S6. The administration schedule for metformin and perpetrators.

Perpetrator	Ref.	administration schedule
Cimetidine	[7]	The subjects received a single daily oral dose of 250 mg metformin in addition 400 mg cimetidine twice daily (2 × 200 mg)
Cimetidine	[12]	The subjects received a single oral dose of 400 mg cimetidine and then a single oral dose of 500 mg metformin 2 h later

pyrimethamine	[63]	The subjects received 250 mg metformin 1 h after receiving 50 mg pyrimethamine
pyrimethamine	[63]	The subjects received 0.1 mg metformin 1 h after receiving 50 mg pyrimethamine
pyrimethamine	[14]	500 mg metformin was administered with 50 mg pyrimethamine
trimethoprim	[15]	Metformin 500 mg and trimethoprim 200 mg were administered orally at midnight and at 20:00 on the day before pharmacokinetic evaluation study. On study day, trimethoprim 200 mg was given half an hour before administration of 500 mg metformin
trimethoprim	[30]	850 mg metformin and 200 mg trimethoprim were administered orally in the evening (20:00) on the day before pharmacokinetic evaluation study and in the morning of study day (8:00)
ondansetron	[31]	The subjects received 850 mg metformin 1 h after receiving 8 mg ondansetron
rabeprazole	[10]	The first dose of metformin (1000 mg) was taken orally on the day before study day at 20:00 PM, and the second dose (750 mg) metformin together with rabeprazole or placebo was given on study day at 8:00 AM with a 12 h interval
rabeprazole	[25]	At 8 PM the participants were given metformin (750 mg by mouth). The following day at 8 AM the subjects were given metformin 500 mg (by mouth) with rabeprazole
verapamil	[23]	750 mg metformin was administered with 180 mg verapamil

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