Physiologically Based Pharmacokinetic Modeling of Metformin in Children and Adolescents with Obesity: Supplemental Tables

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Table S1. Drug specific parameters from the published adult metformin PBPK model adopted for use in children and adolescents.

Parameter	Value	Unit
Physiochemical properties		
Molecular weight	129.16	g/mol
pK_{a1} (base)	2.8	
pK_{a2} (base)	11.5	
Solubility (pH 6.8)	350.90	g/l
Log *P*	-1.43	
*F*u	100	%
ADME [a]		
PMAT K_m	367.57	µmol/l
PMAT V_{max}	76.47	µmol/l/min
PMAT Hill	3.0	
OCT1 K_m	1180.0	µmol/l
OCT1 V_{max}	641.19	µmol/l/min
OCT2 K_m	810.0	µmol/l
OCT2 V_{max}	5.17E+04	µmol/l/min
MATE1 K_m	283.0	µmol/l
MATE1 V_{max}	165.69	µmol/l/min
GFR fraction	1.0	
EHC continuous fraction	1.0	
Cellular permeability [b]	2.30E-04	cm/min
Intestinal permeability (apical)	8.49E-07	cm/min
Small intestinal permeability (basolateral)	1.16E-05	cm/min
Large intestinal permeability (basolateral)	0.0	cm/min
Dissolution		
Weibull shape	7.90	
Fasted Weibull time	1.36	min
Fed Weibull time	0.11	min

Parameters were adopted from the adult model[1]; values for the adult model were obtained from the literature, optimized, assumed, or calculated.

[a] Partition coefficients were calculated using PK-Sim Standard calculation method.

[b] Cellular permeability was calculated using charge-dependent Schmitt normalized to PK-Sim calculation method.

EHC, enterohepatic circulation; *f*u, fraction unbound; GFR, glomerular filtration rate; K_m, concentration of half-maximal transport; Log *P*, lipophilicity; MATE1, multidrug and toxin extrusion protein 1; OCT1, organic cation transporter 1; OCT2, organic cation transporter 2; PBPK, physiologically based

pharmacokinetic; pKa, negative log of the acid dissociation constant; PMAT, plasma membrane monoamine transporter; V_{max}, maximal rate of metabolism or transport.

Table S2. System specific parameters used in the metformin PBPK model.

	Reference concentration			
Transporter	Mean	GSD	Localization (primary)	Direction
PMAT	1.0	1.40	Enterocyte (apical); Other tissues (basolateral)	Influx
OCT1	0.16	1.50	Liver (basolateral)	Influx
OCT2	0.19	1.45	Kidney (basolateral)	Influx
MATE1	0.13	1.53	Kidney (apical)	Efflux

Values are mean and GSD reference concentration for the corresponding transporter adopted from Hanke et al.[1]; GSD was added to population simulations to account for transporter variability.
GSD, geometric standard deviation; MATE1, multidrug and toxin extrusion 1; OCT1, organic cation transporter 1; OCT2, organic cation transporter 2; PBPK, physiologically based pharmacokinetic; PMAT, plasma membrane monoamine transporter.

Table S3. Observed pharmacokinetic parameters calculated for three populations of children and adolescents.

Parameter	Non-overweight [a]	Overweight / obesity [b]	Severely obesity [c]
C_{max} (mg/L) [d]	3.49 ± 1.06 (2.64 – 4.69)	1.65	2.99 ± 1.36 (1.17 – 8.10)
AUC (h*mg/L) [d]	24.4 ± 7.65 (16.6 – 31.8)	9.46	15.5 ± 6.96 (7.15 – 40.8)
CL/F (mL/min)	573 ± 193 (408 – 785)	1374	970 ± 346 (319 – 1817)
V/F (L)	170 ± 68.7 (116 – 247)	379	328 ± 158 (71.7 – 766)

[a] Mean ± SD (range) for parameters estimated using digitized concentration-time profiles including two individual subjects and median concentrations for four children.[2]
[b] Values calculated using median plasma concentrations for 22 adolescents.[3]
[c] Mean ± SD (range) for parameters calculated using concentration-time profiles for 29 children and adolescents[4]; one subject was excluded due to missing data.
[d] AUC calculated over the dosing interval at steady state; values normalized to 1000 mg dose.
AUC, area under the concentration-time curve calculated over the dosing interval at steady state; CL/F, oral clearance calculated as dose (mg) divided by AUC; C_{max}, maximum plasma concentration of metformin at steady state; V/F, apparent volume of distribution calculated as CL/F divided by the elimination rate constant.

Table S4. Observed and predicted model results for children and adolescents classified as non-overweight and having overweight / obesity.

Group	n	Dose (mg)	C_{max} (mg/L)			AUC (h*mg/L)			CL/F (mL/min)			V/F (L)		
			Obs	Pred	Ratio	Obs	Pred	Ratio	Obs	Pred	Ratio	Obs	Pred	Ratio
Non-Overweight [a]														
LD	1	425, qd	1.12	1.16	1.03	7.04	7.45	1.06	785	742	0.94	247	208	0.84
ID	4	850, qd	2.67	1.86	0.70	21.0	11.2	0.53	526	985	1.9	146	235	1.6
HD	1	850, qd	3.98	2.14	0.54	27.1	13.5	0.50	408	818	2.0	116	210	1.8
Overweight / obesity [b]														
Median	22	1000, bid	1.65	2.19	1.3	9.46	12.6	1.3	1374	1028	0.75	379	284	0.75

Values are observed and predicted pharmacokinetic parameters derived either using concentration-time data for individual subjects, or the mean or median concentration-time profile for a group of subjects, as well as the ratio of predicted / observed values.

AUC, area under the concentration-time curve calculated over the dosing interval at steady state; CL/F, oral clearance calculated as dose (mg) divided by AUC; C_{max}, maximum plasma concentration of metformin at steady state; V/F, apparent volume of distribution calculated as CL/F divided by the elimination rate constant.

[a] Concentration data were divided into 3 groups based on the published study[2]: one girl who received the lowest metformin dose (425 mg; 13 mg/kg), one girl who received the highest metformin dose when normalized to body weight (850 mg; 37 mg/kg), and the mean of 4 girls who received intermediate doses when normalized to body weight (850 mg; 21 – 29 mg/kg).

bid, twice daily; HD, highest dose; ID, intermediate dose; LD, lowest dose; Obs, observed; Pred, predicted; qd, once daily.

[b] Concentration data were digitized as the median of 22 children.[3]

REFERENCES

1. Hanke N, Türk D, Selzer D, et al. A comprehensive whole-body physiologically based pharmacokinetic drug–drug–gene interaction model of metformin and cimetidine in healthy adults and renally impaired individuals. *Clin Pharmacokinet*. 2020;59(11):1419–31.
2. Sánchez-Infantes D, Díaz M, López-Bermejo A, Marcos MV, de Zegher F, Ibáñez L. Pharmacokinetics of metformin in girls aged 9 years. *Clin Pharmacokinet*. 2011;50(11):735–8.
3. van Rongen A, van der Aa MP, Matic M, et al. Increased metformin clearance in overweight and obese adolescents: a pharmacokinetic substudy of a randomized controlled trial. *Pediatr Drugs*. 2018;20(4):365–74.
4. Sam WJ, Roza O, Hon YY, et al. Effects of SLC22A1 polymorphisms on metformin-induced reductions in adiposity and metformin pharmacokinetics in obese children with insulin resistance. *J Clin Pharmacol*. 2017;57(2):219–29.