

Supplemental Data

Journal Title

Drug Metabolism and Disposition

Article Title

Investigating the role of altered systemic albumin concentration on the disposition of theophylline in adult and pediatric asthma patients by using the physiologically based pharmacokinetic approach

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Supplemental Table 1 Drug-specific input parameters used for model development

Parameter	Value	Method/Reference	
Molecular weight (g/mol)	180.167	(Edginton et al., 2006)	
Log $P_{o:w}$	-0.02	(Edginton et al., 2006)	
pK _a	8.81	Simcyp® simulator compound library	
pK _a	0.99		
Compound type	Ampholyte		
Main plasma binding protein	HSA		
Absorption Model	ADAM Model		
P _{eff,man} (cm/s)	4.2×10 ⁻⁴	Simcyp® simulator compound library	
f _{uGut}	0.88	Predicted in Simcyp®	
Distribution Model	Minimal PBPK		
V _{ss} (L/kg)	0.45	Simcyp® Prediction Method 1 (Poulin and Theil/ Berezhkovskiy method)	
B/P ratio	0.85	(Ebden et al., 1986)	
f _u	0.61	(Obach et al., 2008)	
Elimination			
CL _R (L/h)	0.31	Simcyp® simulator compound library	
Enzymes			
CYP1A2	V _{max} ^a	4.11 ^c , 2.47 ^d , 6.0 ^e	Simcyp® simulator compound library
	K _m ^b	394 ^c , 1080 ^d , 377 ^e	
CYP2D6	V _{max} ^a	1.8 ^e , 4.68 ^c	
	K _m ^b	6897 ^e , 10709 ^c	
CYP3A4	V _{max} ^a	0.4 ^c	
	K _m ^b	23393 ^c	
CYP2E1	V _{max} ^a	40.78 ^c	
	K _m ^b	16855 ^c	

Log $P_{o:w}$; octanol-water partition coefficient, ADAM; advanced dissolution, absorption and metabolism, HSA; Human serum albumin, P_{eff}; effective human jejunum permeability, f_u; the fraction of unbound drug in plasma, f_{uGut}; the unbound fraction of drug in enterocytes, V_{ss}; the volume of distribution at steady-state, CL_R; renal clearance, CYP; cytochrome P-450 enzyme.

^a Maximum rate of metabolite formation, units: pmol/min/pmol of isoform

^b Michaelis-Menten constant, units: μMol

^c 8-OH pathway

^d N1-demethylation pathway

^e N3-demethylation pathway

Supplemental Table 2 Characteristics of clinical data used for model development in healthy adults

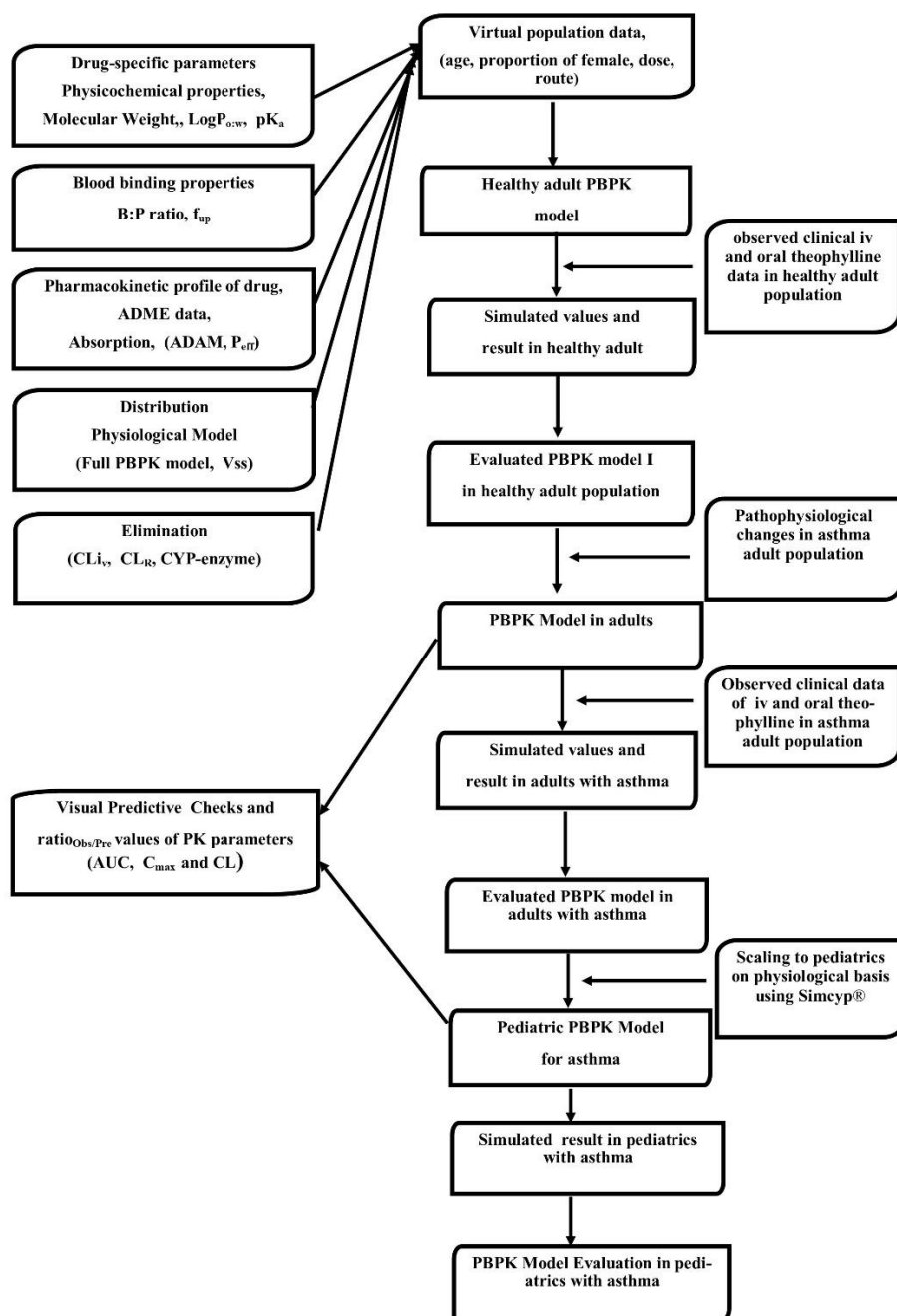
No	Population	No. of subjects	Dose	Administration route	Age (years)	Weight (kg)	Female proportion	Reference
1	Healthy	6	2.78 mg/kg	iv bolus	Range 25–32	-	0	(Ishizaki et al., 1979)
	Healthy	6	4 mg/kg	iv bolus	Range 25–32	-	0	(Ishizaki et al., 1979)
2	Healthy	6	3.84 mg/kg	iv infusion	Range 24–57	-	0	(Chrzanowski et al., 1977)
3	Healthy	8	6 mg/kg	iv bolus	Range 18–25	Mean 70.6	0	(St-Pierre et al., 1985)
4	Healthy	4	193.2 mg	iv bolus	Range 24–26	Range 50-70	0.75	(Gundert-Remy et al., 1983)
	Healthy	4	386.4 mg	iv bolus	Range 24-26	Range 50-70	0.75	(Gundert-Remy et al., 1983)
5	Healthy	8	125 mg	Oral	Range 22–35	Mean 62	0.5	(Rovei et al., 1982)
	Healthy	8	250 mg	Oral	Range 22–35	Mean 62	0.5	(Rovei et al., 1982)
	Healthy	8	375 mg	Oral	Range 22–35	Mean 62	0.5	(Rovei et al., 1982)
	Healthy	8	500 mg	Oral	Range 22–35	Mean 62	0.5	(Rovei et al., 1982)
6	Healthy	14	200 mg	Oral	Range 70–85	Mean 76	0.92	(Antal et al., 1981)
	Healthy	14	200 mg	Oral	Range 19-31	Mean 23	0.92	(Antal et al., 1981)
7	Healthy	1	250 mg	Oral	22	68	0	(Lagas and Jonkman, 1983)
	Healthy	1	250 mg	Oral	24	85	0	(Lagas and Jonkman, 1983)
8	Healthy	6	600 mg	Oral	Range 18–65	-	-	(Gonzalez and Golub, 1983)
	Healthy	6	600 mg	Oral	Range 18–65	-	-	(Gonzalez and Golub, 1983)
9	Healthy	6	250 mg	Oral	Range 19–21	Range 62-104	0	(Lelo et al., 1986)

Supplemental Table 3 Characteristics of clinical data used for model development in adults and children with asthma

No.	Population	No. of subjects	Dose	Administration route	Age (years)	Weight (kg)	Female proportion	Reference
Adult population								
1	Asthma	7	5.6 mg/kg	iv bolus	Range 34-53	-	0.5	(Mitenko and Ogilvie, 1973)
2	Asthma	50	351 mg	iv infusion	Range 17-80	Range 51-97	0.4	(Steinijans et al., 1982)
3	Asthma	31	7.5 mg/kg	Oral	Range 20-60	-	-	(Weinberger and Hendeles, 1986)
4	Asthma	46	600	Oral	Range 45-49	Range 55.7-63.1	0.5	(Richer et al., 1982)
Pediatric population								
3	Asthma	10	3.2 mg/kg	iv infusion	Range 1-4	Range 9.3-16.4	0.5	(Loughnan et al., 1976)
4	Asthma	12	4 mg/kg	iv bolus	Range 6-10	-	0.36	(Ellis et al., 1976)
5	Asthma	40	8.2 mg/kg	Oral	Range 4-12	-	-	(Hendeles L, 1985)

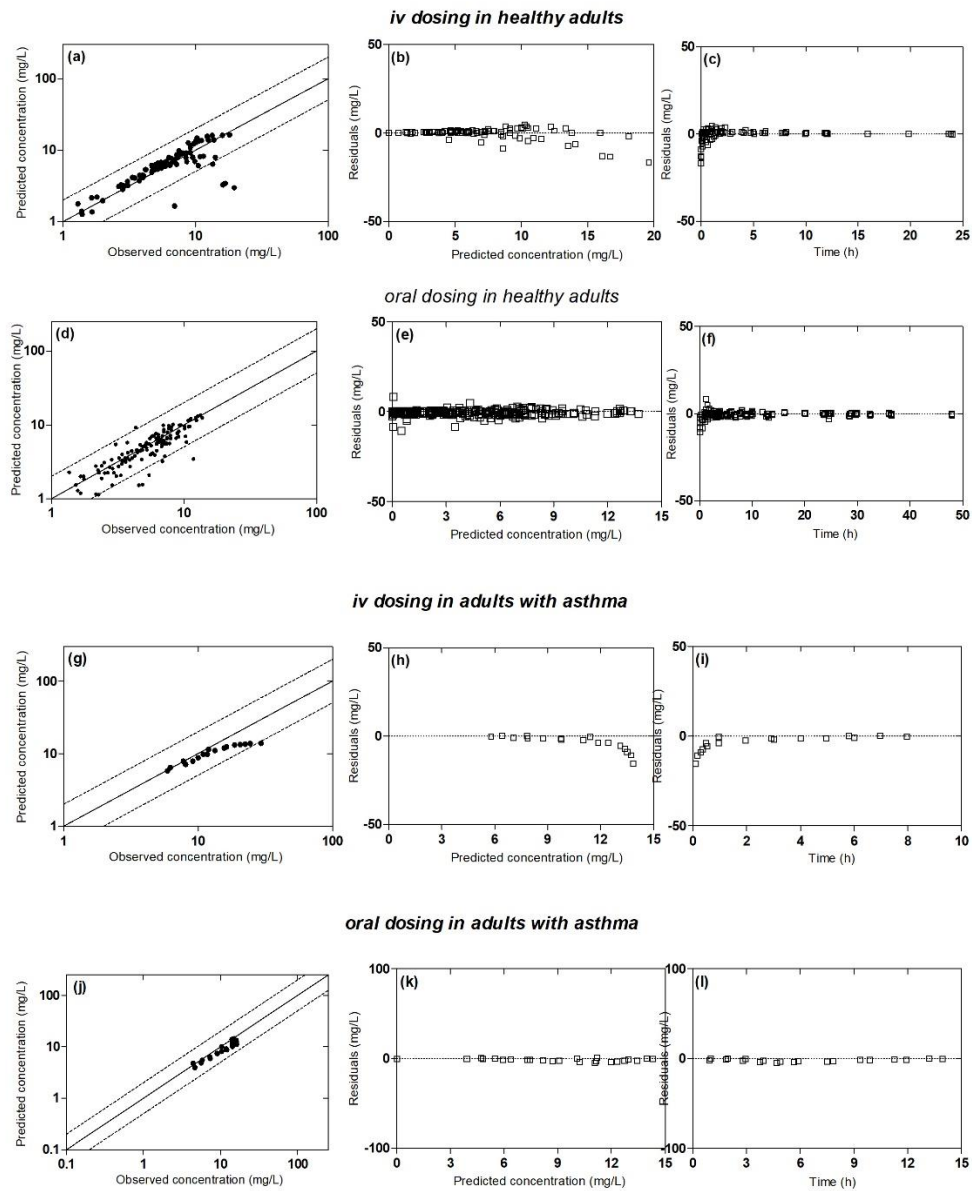
Supplemental Table 4 The observed/predicted ratio ($R_{obs/Pred}$), average fold error (AFE) and root mean square error (RMSE) values for pharmacokinetic parameters in adults and children after intravenous and oral theophylline application

Parameters	Ratio_{obs/pred}	AFE	RMSE
Intravenous application in healthy adults			
AUC _{0-∞}	0.90	0.90	8.90
CL	1.21	1.16	0.01
C _{max}	1.60	1.66	5.85
Oral application in healthy adults			
AUC _{0-∞}	1.05	1.04	23.26
CL	1.01	0.99	0.58
C _{max}	1.06	1.05	1.10
Adults with asthma (intravenous & oral)			
AUC _{0-∞}	1.21	1.21	19.92
CL	0.94	0.93	0.42
C _{max}	1.48	1.43	8.54
Children with asthma (intravenous & oral)			
AUC _{0-∞}	0.92	0.92	5.64
CL	1.39	1.37	0.03
C _{max}	1.16	1.16	1.75



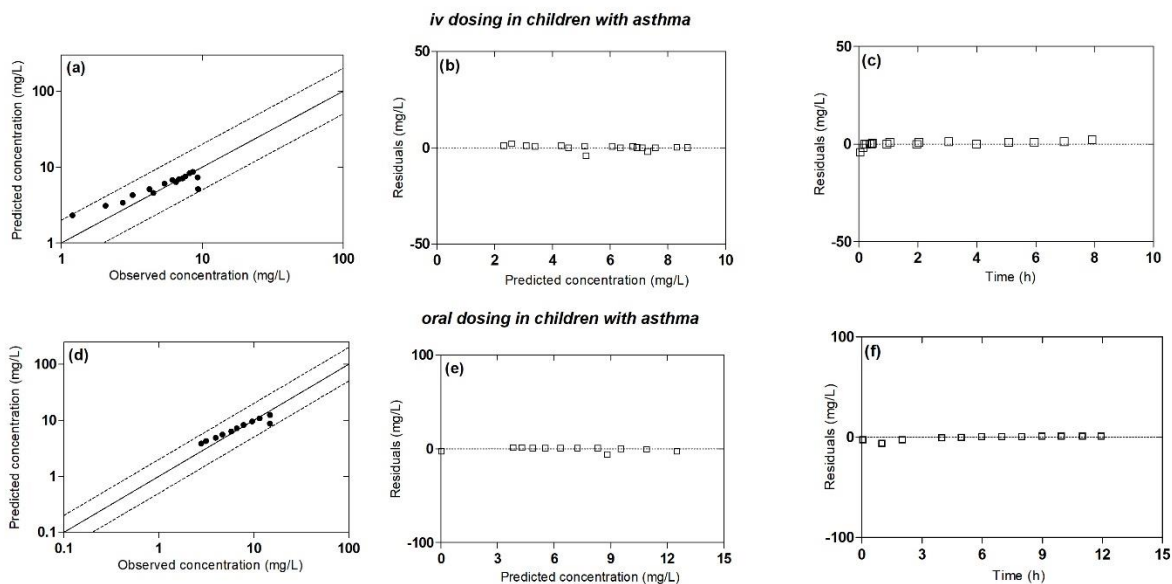
Supplemental Figure 1 Workflow diagram for developing physiologically based pharmacokinetic (PBPK) model in healthy and asthma (adult and pediatric) population.

Where ADAM: advanced, dissolution, absorption and metabolism, $\text{Log } P_{o:w}$: octonal-water partition coefficient, pK_a : acid dissociation constant, $P_{\text{eff,man}}$: human jejunum permeability, f_{up} : fraction of unbound drug in plasma, CL_{IV} : intravenous clearance, CL_R : renal clearance, CYP: cytochrome P450, $AUC_{0\text{-last}}$: Area under the drug concentration time curve from zero to last measured drug concentration time, C_{max} : maximum concentration of drug



Supplemental Figure 2 Goodness-of-fit plots for model prediction in adult population.

presented as: (a,d,g,j) plot of predicted versus observed concentration; (b,e,h,k) plots of residual versus predicted concentration; (c,f,i,l) plots of residual versus time; (a-c) iv and (d-f) oral dosing in healthy adult population, (g-i) iv and (j-l) oral dosing in asthma adults. Solid lines show line of identity and dashed line show 2-fold error range



Supplemental Figure 3 Goodness-of-fit plots for model prediction in pediatric population.

presented as: (a,d) plot of predicted versus observed concentration; (b,e) plots of residual versus predicted concentration; (c,f) plots of residual versus time; (a-c) iv and (d-f) oral dosing in children population with asthma. Solid lines show line of identity and dashed line show 2-fold error range.

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