A PBPK Model to Predict Disposition of P450 2D6 and P450 1A2 Metabolized Drugs in Pregnant Women

A.B. Ke, S.C. Nallani, P. Zhao, A. Rostami-Hodjegan, N Isoherranen, J. D. Unadkat

Supplemental Materials

Supple. Table 1 Theophylline PK Parameters (259 mg p.o.) during T_3 and Postpartum

	Observed	Predicted	Predicted/Observed
AUC_{0-8} (mg/L•hr)			
Pregnancy (T_1)	94.6[a]	109.9	1.2
Pregnancy (T_2)	98.8[a]	113.8	1.2
Pregnancy (T_3)	125.5[a]	114.3	0.9
Postpartum (PP)	93.6[b]	87.1	0.9
AUC_{PP}/AUC_{T1}	0.99	0.79	0.8
AUC_{PP}/AUC_{T2}	0.95	0.77	0.8
AUC_{PP}/AUC_{T3}	0.75	0.76	1.0
C_{max} (mg/L)			
Pregnancy (T_1)	12.9	14.6	1.1
Pregnancy (T_2)	13.0	14.7	1.1
Pregnancy (T_3)	14.0	14.3	1.0
Postpartum (PP)	12.4	13.6	1.1
$C_{max,PP}/C_{max,T1}$	0.96	0.93	1.0
$C_{max,PP}/C_{max,T2}$	0.95	0.92	1.0
$C_{max,PP}/C_{max,T3}$	0.89	0.95	1.1
$C_{min,8h}$ (mg/L)			
Pregnancy (T_1)	7.4	7.5	1.0
Pregnancy (T_2)	7.6	8.0	1.0
Pregnancy (T_3)	9.4	8.1	0.9
Postpartum (PP)	6.8	5.4	0.8
$C_{min,PP}/C_{min,T1}$	0.91	0.71	0.8
$C_{min,PP}/C_{min,T2}$	0.89	0.67	0.8
$C_{min,PP}/C_{min,T3}$	0.72	0.66	0.9

[a]: AUC estimates based on observed concentration data (Gardner et al., 1987) were generated using linear trapezoidal rule

[b]: Oral clearance (CL_{ORAL}) was found to remain suppressed during immediate postpartum period (9-13 wks PP). Therefore, AUC_{0-8} obtained during 14-58 wks postpartum was considered to represent pre-pregnancy levels.

Supple. Table 2 Metoprolol PK Parameters (100 mg p.o.)			
Non-pregnant Population			
	Obs.	Pred.	Pred./Obs.
$AUC_{0\text{-}inf}$ (µg/L•h)			
EM	895.8[a]	1087.1	1.2
PM	4062.8[a]	4507.8	1.1
AUC_{PM}/AUC_{EM}	4.5	4.1	0.9
AUC_{EM+Qd}/AUC_{EM}	3.2[b]	3.3	1.0
C_{max} (µg/L)			
EM	170.9[a]	158.7	0.9
PM	427.6[a]	313.7	0.7
$C_{max,PM}/C_{max,EM}$	2.5	2.0	0.8
$C_{min,12h}$ (µg/L)			
EM	19.2[c]	26.7	1.4
PM	133.7[d]	177.6	1.3
$C_{min,PM}/C_{min,EM}$	7.0	6.7	1.0
During T_3 and Postpartum			
	Obs. [e]	Pred. (200% P450 2D6 Ind) [f]	Pred./Obs.
$AUC_{0\text{-}inf}$ (µg/L•h)			
Pregnancy (T_3)	266.9	302.6	1.1
Postpartum (PP)	952.5	906.3	1.0
AUC_{PP}/AUC_{T3}	3.6	3.0	0.8
C_{max} (µg/L)			
Pregnancy (T_3)	49	51.8	1.1
Postpartum (PP)	168	142.7	0.8
$C_{max,PP}/C_{max,T3}$	2.4	2.8	0.8
$C_{min,12h}$ (µg/L)			
Pregnancy (T_3)	9.8	5.9	0.6
Postpartum (PP)	19.5	21.3	1.1
$C_{min,PP}/C_{max,T3}$	2.0	3.6	1.8

[a]: arithmetic mean of reported values following administration of 100mg single p.o. dose in healthy volunteers extracted from University of Washington, Metabolism & Transport Drug Interaction Database (no. of subjects =166, no. of studies=8 for the EM group and no. of subjects =20, no. of studies=3 for the PM group).

[b]: reported (Johnson and Burlew, 1996)

[c]: arithmetic mean of reported values (Hogstedt et al., 1985; Hamelin et al., 2000; Sharma et al., 2005).

[d]: arithmetic mean of reported values (Hamelin et al., 2000; Sharma et al., 2005).

[e]: arithmetic mean values reported by Hogstedt et al. (Hogstedt et al., 1985).

[f]: refers to 200% induction of P450 2D6

Supple. Table 3 Paroxetine PK Parameters in Non-pregnant Population						
Parameters	30 mg SD			30mg QD		
$AUC_{0\text{-}inf}$ or $AUC_{ss,0\text{-}tau}$ µg/L•h	Obs.[a]	Pred.	Pred./ Obs.	Obs.[a]	Pred.	Pred./ Obs.
EM	187.3	154.8	0.8	893.1	884.2	1.0
PM	1321.7	1627.9	1.2	1536.6	1703.2	1.1
AUC_{PM}/AUC_{EM}	7.1	10.5	1.5	1.7	1.9	1.1
C_{max} (µg/L)						
EM	7.9	9.1	1.2	52.4	46.9	0.9
PM	22.7	28.8	1.3	77.5	83.2	1.1
$C_{max,PM}/C_{max,EM}$	2.9	3.2	1.1	1.5	1.8	1.2
$C_{min,24h}$ (µg/L)						
EM	2.7	2.1	0.8	26.5	25.7	1.0
PM	14.5	18.9	1.3	54.2	56.5	1.0
$C_{min,PM}/C_{min,EM}$	5.4	9.1	1.7	2.0	2.2	1.1

[a]: arithmetic mean of reported values (Sindrup et al., 1992b)

Supple. Table 4	Paroxetine $C_{ss, average}$ (20mg QD) in P450 2D6 EMs during T_3 and PP				
$C_{ss, average}$ (ng/mL)	Obs. Median	Pred.[c] (200% P450 2D6 Ind) [d]	Pred. /Obs.	Pred. (100% P450 2D6 Ind) [d]	Pred. /Obs.
Non-pregnant	18.4[a]	18.1	1.0	18.1	1.0
Pregnancy (T_3)	5.0[b]	2.5	0.5	4.4	0.9
C_{ss} ratio (PP:T_3)	3.7	7.1	1.9	4.1	1.1

[a] The concentrations measured 12 hours ($\tau/2$) after dosing were taken as an approximation to mean C_{ss} (Sindrup et al., 1992a).

[b] Reported median values (Ververs et al., 2009). Time between drug intake and sample collection varied.

[c] Predicted concentration at $\tau/2$ was taken as an approximation to mean $C_{ss.}$

[d] Refers to 200% induction and 100% induction of P450 2D6.

Supple. Table 5 Dextromethorphan PK Parameters (30 mg p.o.) in Non-pregnant Population			
	Obs.	Pred.	Pred./ Obs.
$AUC_{0\text{-}inf}$ (μg/L•h)			
EM	16.9[a]	16.3	1.0
PM	1241.6[b]	1058.8	0.9
EM+Qd	350.8[c]	258.7	0.7
AUC_{PM}/AUC_{EM}	73.5	65.0	0.9
AUC_{EM+Qd}/AUC_{EM}	20.8	15.9	0.8
C_{max} (μg/L)			
EM	2.0[a]	1.8	0.9
PM	23.1[b]	29.7	1.29
EM+Qd	19.5[c]	21.0	1.1
$C_{max,PM}/C_{max,EM}$	12.1	16.5	1.4
$C_{max,EM+Qd}/C_{max,EM}$	10.2	11.6	1.1
$C_{min,48h}$ (μg/L)			
EM	0.2[a]	0.04	0.2
PM	10.7[b]	8.94	0.8
EM+Qd	2.0[c]	0.9	0.5
$C_{min,PM}/C_{min,EM}$	58.9	223.5	3.8
$C_{min,EM+Qd}/C_{min,EM}$	11.0	22.5	2.0

[a]: Weighted arithmetic mean of reported values following administration of 30 mg single p.o. dose (Capon et al., 1996; Abdul Manap et al., 1999; Gorski et al., 2004; Abduljalil et al., 2010)

[b]: Weighted arithmetic mean of reported values following administration of 30 mg single p.o. dose (Capon et al., 1996; Gorski et al., 2004)

[c]: Weighted arithmetic mean of reported values following administration of 30 mg single p.o. dose (Capon et al., 1996; Abdul Manap et al., 1999)

Supple. Table 6	DEX UR in 2D6 EMs during T_3 and Postpartum				
$UR_{0\text{-}24h}$ (DEX/DXO)	Obs. [a]	Pred. (200% P450 2D6 Ind)	Pred./Obs.	Pred. (100% P450 2D6 Ind)	Pred./Obs.
Pregnancy (T_3)	0.0033	0.0023	0.7	0.0034	1.0
	(0.00147-0.0086)	-		-	
Postpartum (PP)	0.0063	0.0065	1.0	0.0065	1.0
	(0.0037-0.026)	-		-	
UR_{PP}/UR_{T3}	1.9	2.9	1.5	1.9	1.0

[a]: Reported median (90% CI) following the administration of 30 mg single p.o. dose (Tracy et al., 2005)

Supple. Table 7 Clonidine PK Parameters in Non-pregnant Population			
	Obs.	Pred.	Pred./ Obs.
$AUC_{0\text{-}inf}$ (µg/L•h)			
2.35 µg/Kg i.v.	11.3[a]	12.5	1.1
1.79 µg/Kg i.v.	8.1[a]	9.5	1.2
$C_{min,\ 24h}$ (µg/L)			
2.35 µg/Kg i.v.	0.35[a]	0.156	0.4
1.79 µg/Kg i.v.	0.12[a]	0.12	1.0
$AUC_{0\text{-}inf}$ (µg/L•h)			
0.1 mg p.o.	7.3[b]	6.3	0.9
0.2 mg p.o.	14.3[c]	12.5	0.9
0.3 mg p.o.	21.5[d]	18.8	0.9
C_{max} (µg/L)			
0.1 mg p.o.	0.44[b]	0.44	1.0
0.2 mg p.o.	0.88[c]	0.88	1.0
0.3 mg p.o.	1.4[d]	1.32	0.9
$C_{min,\ 24h}$ (µg/L)			
0.1 mg p.o.	0.1[b]	0.08	0.8
0.2 mg p.o.	-	0.16	-
0.3 mg p.o.	0.3[d]	0.25	0.8

[a]: reported mean values (Frisk-Holmberg et al., 1981)

[b]: reported mean values extracted from product label for CATAPRES® (Clonidine Hydrochloride) oral tablet.

[c]: reported mean values(Porchet et al., 1992)

[d]: reported mean values (Cunningham et al., 1994)

Supple. Table 8 Clonidine PK Parameters during T_3 and Postpartum					
	Obs. [a]	Pred. (200% P450 2D6 Ind)	Pred./Obs.	Pred. (100% P450 2D6 Ind)	Pred./Obs.
$AUC_{0\text{-}tau}$ (µg/L•hr)					
Pregnancy (T_3)	5.7	4.8	0.8	5.8	1.0
Postpartum (PP)	9.6	10.4	1.1	10.4	1.1
AUC_{PP}/AUC_{T3}	1.7	2.2	1.3	1.8	1.1
C_{max} (µg/L)					
Pregnancy (T_3)	0.57	0.61	1.1	0.7	1.2
Postpartum (PP)	-	1.18	-	1.18	-
$C_{max,PP}/C_{max,T3}$	-	1.9	-	1.7	-

[a] Observed value calculated based on reported CL_{ORAL} and assumed mean dose of 0.15 mg (dose range: 0.15-0.3 mg per day) (Buchanan et al., 2009).