Development of an Open-source Physiologically-based Pharmacokinetic Model to Predict Maternal-fetal Exposures of CYP450-metabolized Drugs

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Abstract

Background: Pregnancy causes extensive physiological changes impacting drug exposure in mother and fetus. Predicting a drug's pharmacokinetic (PK) profile is crucial to ensuring safe and efficacious dosing during pregnancy. Conducting clinical PK trials in pregnancy, however, is both logistically and ethically challenging. Physiologically-based (PB) PK models can provide *in silico* predictions of drug exposures during pregnancy by accounting for known physiologic changes. These models can guide dosing prior to drug administration and refine dosing once initial exposures are determined.

Methods: Maternal-fetal and non-pregnant PBPK models were developed (R, mrgsolve [**1**]) to predict maternal/fetal exposure of drugs primarily metabolized by liver CYP450 enzymes (3A4, 2D6, 1A2, 2B6). Model parameters, initially based on literature, were refined using sensitivity analyses followed by parameter optimization. Models were validated by comparing observed and predicted PK profiles of 10 drugs: midazolam, metoprolol, caffeine, nifedipine, nevirapine, artemether, indinavir, buprenorphine, codeine and methadone.

Results: The relative error (RE) in predicted estimates of area under the curve (AUC) and peak plasma concentration (C_{max}) across all tested drugs were 0.17 - 33.1% for AUC and 1.57 - 50.7% for C_{max} in the non-pregnant model and 3.34 - 38.1% (AUC) and 7.88 - 23.8% (C_{max}) in the pregnant model. Sensitivity analyses and parameter optimization further improved model predictions of these PK parameters.

Conclusions: The described PBPK model provides a reproducible, open-source system for model-informed decision for exploring and developing exposure-based dosing recommendations in maternal/fetal patient populations. Inclusion of individual genotype data may further improve the modeling.

Methods

Maternal/Fetal PBPK Model Structure and Workflow

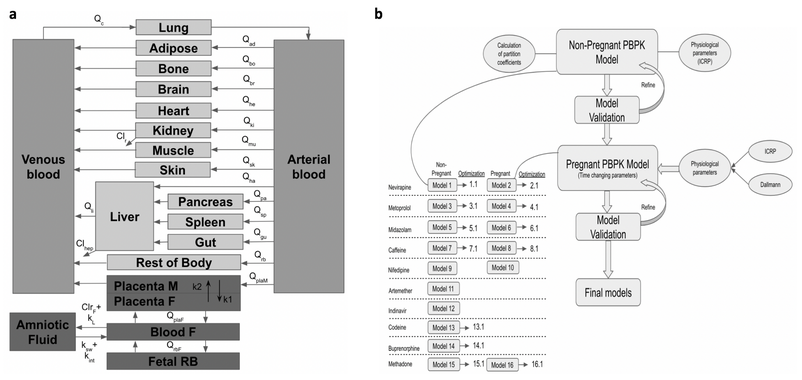

Fig.1 (a) Flow-limited full PBPK model structure. (b) Model development workflow. Q represents the blood flows and Cl represents clearance while the subscripts ad, bo, br, gu, ha, he, ki, li, lu, mu, sp, rb, $plaM$, $plaF$, rbF refer to adipose, bone, brain, gut, hepatic artery, heart, kidneys, liver, lungs, muscle, spleen, rest of the body, maternal placenta, fetal placenta and fetal rest of the body compartments, respectively. Cl_{hep}, Cl_r, Q_c, Clr_F, k_{sw}, k_{int} and k_L refer to the hepatic artery, hepatic clearance, renal clearance, cardiac output, fetal renal clearance, swallowing constant, intramembranous pathway and lung excretion.

Gestational-age dependent formula [2]

$$X_P = X_0(a_0 + a_1 GA + a_2 GA^2 + a_3 GA^3)$$

where GA is gestational age and the subscript P refers to the parameter of interest. Hepatic intrinsic clearance was calculated by evaluating the activities of the enzymes of interest as shown in the equation above and then substituting these in:

$$Cl_{int} = Cl_{int,0}(\alpha_{1A2}.X_{1A2} + \alpha_{2D6}.X_{2D6} + \alpha_{3A4}.X_{3A4} + \alpha_{2B6}.X_{2B6} + other)$$

where $Cl_{int,0}$ is the initial value for intrinsic clearance, X_{1A2}, X_{2D6}, X_{3A4} and X_{2B6} refer to the activities of the respective enzymes CYP1A2, 2D6, 3A4 and 2B6. α parameters refer to the fractional contributions of each enzyme. The major enzymatic contributions to drug metabolism were:

- CYP1A2: Caffeine (1).
- CYP2D6: Metoprolol (0.93), Nevirapine (0.118), Codeine.
- CYP3A4: Midazolam (1), Nifedipine (1), Nevirapine (0.464), Methadone (0.412), Artemether, Buprenorphine, Indinavir, Metoprolol (0.07).
- CYP2B6: Nevirapine (0.275), Methadone (0.563), Artemether.

*Fractional contributions for drugs that were implemented in the pregnant model are shown in brackets.

Model Evaluation

Model evaluations included visual inspection of a longitudinal overlay of predicted and observed data for each drug. Derived PK parameters (AUC, C_{max}) were also compared between the predicted and observed concentration-time profiles; precision and bias were quantified through residual error calculations.

Results

Comparing Observed and Predicted Concentration-Time Profiles for 10 drugs

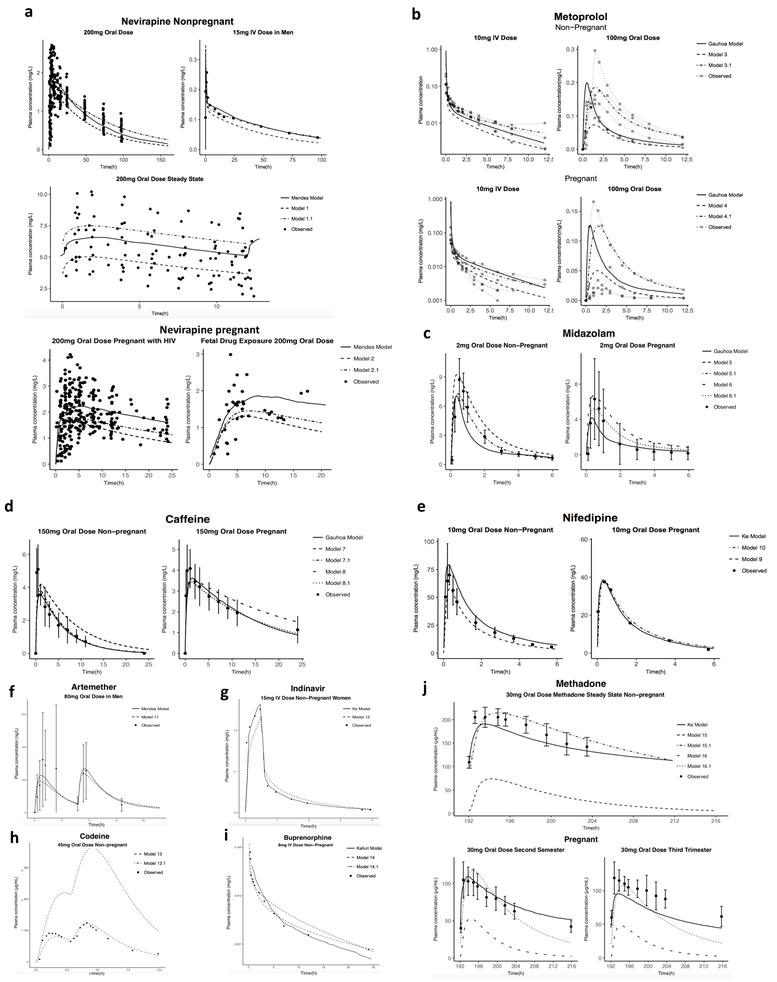

Fig.2 Observed plasma concentration-time profiles compared to our predictions and previously published ones for (a) caffeine, (b) midazolam, (c) metoprolol, (d) nifedipine, (e) nevirapine, (f) artemether, (g) indinavir, (h) codeine, (i) buprenorphine, and (j) methadone. Observed data are mean values except for metoprolol and nevirapine. Sources for observed data and previously published predictions are [**2-11**]. Error Bars represent standard deviation.

Table 1 Parameter optimization using maximum likelihood estimation and *nloptr* package [**6**].

Drug	Parameter	Original	Optimized
Nevirapine	Kp_{ad}	2.62	2.4
	Kp_{li}	1.674	1.067
Metoprolol	Kp_{li}	4.205	1.066
	F_a	0.88	0.85
	$T_{lag}\ (h)$	*NA*	0.769
Midazolam	Kp_{gu}	2.213	4.2
	Kp_{li}	1.711	2.53
	$K_a\ (h^{-1})$	3.04	3.5
	Rab	*NA*	0.479
Caffeine	Kp_{li}	0.714	1.09
Codeine	Kp_{li}	0.965	4.245
	Kp_{mu}	0.676	0.126
	$T_{lag}\ (h)$	*NA*	2.833
Buprenorphine	Kp_{ad}	*NA*	0.06
	Kp_{bo}	10.389	35.33
	Kp_{mu}	2.12	0.128
Methadone	Kp_{li}	6.649	1.15

Table 2 Comparison of observed and predicted PK parameters.

	Population	ROI	AUC			C_{max}		
			Obs	Sim	RE (%)	Obs	Sim	RE (%)
Nevirapine	Male	IV (15 mg)	7.9	7.26	8.11	NA	NA	NA
	Non-pregnant	PO (200 mg)	96.9	95.3	1.74	1.81	1.78	1.75
		PO (SS, 200 mg)	66.3	82.4	24.3	10.2	7.5	26.5
	Pregnant	PO (200 mg)	40	36.6	8.52	2.25	1.8	19.9
	Fetus	PO (200 mg)	24.3	36.6	50.5	2.99	1.8	39.6
Metoprolol	Non-pregnant	IV (10 mg)	0.159	0.159	0.183	NA	NA	NA
	Pregnant	IV (10 mg)	0.085	0.0975	14.7	NA	NA	NA
	Non-pregnant	PO (100 mg)	0.857	1.1	27.9	0.167	0.186	11.1
	Pregnant	PO (100 mg)	0.276	0.67	142	0.0687	0.124	80.3
Midazolam	Non-pregnant	PO (2 mg)	15.3	15	1.72	8.73	7.18	17.8
	Pregnant	PO (2 mg)	8.4	11.6	38.2	6.32	5.01	20.7
Caffeine	Non-pregnant	PO (150 mg)	25.6	25.8	0.796	5.1	3.79	25.6
	Pregnant	PO (150 mg)	50.5	48.7	3.6	4.08	3.39	17
Nifedipine	Non-pregnant	PO (10 mg)	127	108	14.9	70.1	57.7	17.6
	Pregnant	PO (10 mg)	76.8	68.7	10.5	37.6	34.6	7.88
Artemether	Male	PO (80 mg)	1420	1280	9.74	162	118	27.2
Indinavir	Non-pregnant	PO (15 mg)	0.208	0.209	0.174	0.251	0.234	6.9
Codeine	Non-pregnant	PO (45 mg)	665	681	2.48	125	122	2.09
Buprenorphine	Male	IV (8 mg)	0.087	0.102	17.3	NA	NA	NA
Methadone	Non-pregnant	PO (30 mg)	3540	3690	4.25	205	214	4.39
	Pregnant (2nd trimester)	PO (30 mg)	1610	1680	4.36	105	120	14.6
	Pregnant (3rd trimester)	PO (30 mg)	2070	1600	22.7	119	114	3.71

Conclusion

- A maternal/fetal flow-limited PBPK model was developed in the open-source freely available R package *mrgsolve* and gestational-age dependent parameters including 4 of the main CYP450 enzyme activities (CYP1A2, CYP2D6, CYP3A4 and CYP2B6) were successfully integrated.
- Model evaluations indicated general goodness-of-fit for each drug and (combinations of) metabolizing enzymes. Parameter optimizations markedly improved the predictions. Thus, the PBPK model, in conjunction with relatively limited plasma PK data for each drug, provided a predictive tool for improved quantification of drug exposure during pregnancy, including longitudinal changes that may further affect PK during pregnancy and fetal growth/development.
- The developed model with its open-source flexible application provides a framework for model-informed exposure-based dosing recommendation in the pregnant woman/fetus special population and conveniently lends itself to further development.

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