Development of an Open-source Physiologically-based Pharmacoki-netic 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.



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.

Model Features

Main features of the model include: (i) Detailed fetoplacental unit [5], (ii) Comprehensive library of equations describing the continuous gestational age-dependent parameter changes including CYP450 enzymatic activity [2, 3], e.g., effect of gestation age (GA) on CYP450 enzymatic activity (Eqn 1):

 $X_P = X_0(a_0 + a_1GA + a_2GA^2 + a_3GA^3)$ where GA is gestational age and the subscript P refers to the CYP450 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:

 $Cl_{int} = Cl_{int,0}(\alpha_{1A2}.X_{1A2} + \alpha_{2D6}.X_{2D6} + \alpha_{3A4}.X_{3A4} + \alpha_{2B6}.X_{2B6} + other)$ (2)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. *Brackets contain fractional contributions (α , Eqn 2) for drugs modeled to include gestational age (Eqn 1).

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.

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Results



Conclusion

- (CYP1A2, CYP2D6, CYP3A4 and CYP2B6) were successfully integrated.
- pregnancy and fetal growth/development.
- lends itself to further development.

References

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• A maternal/fetal flow-limited PBPK model was developed in the open-source freely available R package mrgsolve [1] and gestational-age dependent parameters including 4 of the main CYP450 enzyme activities

• 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

• 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

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Table 1 Parameter optimization using maximum likelihood estimation and *nloptr* package [12].

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

ROA		AUC				
	Obs	Sim	RE (%)	Obs	Sim	RE (%)
V (15 mg)	7.9	7.26	8.11	NA	NA	NA
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
PO (200 mg)	40	36.6	8.52	2.25	1.8	19.9
PO (200 mg)	24.3	36.6	50.5	2.99	1.8	39.6
V (10 mg)	0.159	0.159	0.183	NA	NA	NA
V (10 mg)	0.085	0.0976	14.8	NA	NA	NA
PO (100 mg)	0.857	1.1	27.9	0.167	0.186	11.1
PO (100 mg)	0.276	0.67	143	0.0687	0.125	82.4
PO (2 mg)	15.3	15	1.72	8.73	7.18	17.8
PO (2 mg)	8.4	11.6	38.2	6.32	5.01	17.7
PO (150 mg)	25.6	25.8	0.796	5.1	3.79	25.6
PO (150 mg)	50.5	48.7	3.6	4.08	3.43	15.9
PO (10 mg)	127	108	14.9	70.1	57.7	17.6
PO (10 mg)	76.8	68.7	10.5	37.6	34.5	8.18
PO (80 mg)	1420	1280	9.74	162	118	27.2
V (15 mg)	0.208	0.209	0.174	0.251	0.234	6.9
PO (45 mg)	665	681	2.48	125	122	2.09
V (8 mg)	0.087	0.102	17.3	NA	NA	NA
PO (30 mg)	3540	3690	4.25	205	214	4.39
PO (30 mg)	1610	1680	4.36	105	120	14.6
PO (30 mg)	2070	1600	22.7	119	114	3.71