Application of Lactation Physiologically-Based Pharmacokinetic Modeling to Predict Exposure of Select Compounds

Ruhul Kayesh[1], Michelle Pressly[1], Daphne Guinn[1], Zhoumeng Lin[2], Stephan Schmidt[3], Elimika Pfuma Fletcher[1]

[1]Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA.
[2]Department of Environmental and Global Health, College of Public Health and Health Professions, University of Florida, Gainesville, Florida, USA.
[3]Department of Pharmaceutics, Center for Pharmacometrics and Systems Pharmacology, University of Florida, Orlando, Florida, USA.

Introduction

- One in four mothers are reported to take medications while breastfeeding[1].
- Drugs can pass to an infant through human milk and can potentially cause toxicity depending on the drug and resulting exposure level. Therefore, it is important to estimate the drug excretion in human milk and understand the potential exposure in infants.
- The current study aims to develop and assess the predictive performance of physiologically based pharmacokinetic (PBPK) modeling to predict maternal plasma and milk concentrations.
- The initial 3 drugs evaluated were those with available clinical lactation data and reported to be passively diffused in human milk with varying milk-to-plasma ratio- atenolol, escitalopram and alprazolam[2].

Materials and Methods

Adult PBPK Model Development:

- The adult healthy model was developed for atenolol and escitalopram using the physicochemical and physiological properties of drug.
- The models were verified against published clinical data of:
  - atenolol 25 - 100 mg single dose and a 100mg multiple dose.
  - escitalopram 20mg single dose and a 10mg multiple dose.
- The default compound file in Simcyp V23 library was used for alprazolam PBPK model.

Lactation PBPK Model Development:

- Once the adult healthy PBPK model was established, the lactation PBPK model was constructed by activating the lactation compartment in the Simcyp software.
- The lactation PBPK model was applied to simulate the plasma and milk profile simultaneously and overlaid with the clinical data.
- The infant daily dose (IDD) and relative infant daily dose (RIDD) were calculated by Simcyp V23 software based on following equations:
  - IDD (mg*Kg^{-1}*Day^{-1}) = $C_{average}$ x milk intake (L/day/ infant body weight)
  - RIDD (%) = IDD/(Mother daily dose)x100

Results and Discussion

PBPK Model Verification for Atenolol and Escitalopram

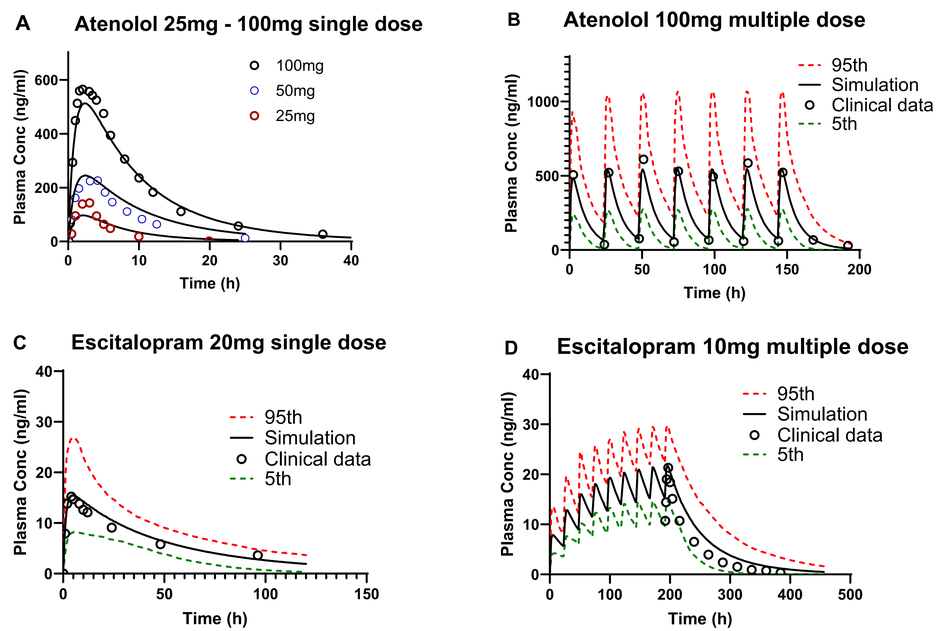

Fig.1. PBPK model verification of atenolol and escitalopram for adult healthy volunteers with respect to clinical data. The solid black line represents the simulated plasma concentration profile and open circles are clinical plasma concentrations. Dashed lines represents 95th (red) and 5th (green) percentile of simulated plasma concentration profile. Model predicted plasma profile of atenolol after single dose oral dose[3-5] (A) and after multiple oral dose[6] (B), and of escitalopram after single oral dose[7] (C) and after multiple oral dose[8] (D).

Table 1. Pharmacokinetics Parameters Predicted by Model vs Observed

Parameter	Milk C_{max} (ng/ml)	Milk AUC (ng/ml*h)	M/P
Atenolol-Predicted	807	6533	2.4
Atenolol-Observed	734	6810	4.7
Escitalopram-Predicted	48.1	1335	1.2
Escitalopram-Observed	64.8	1041	2.2
Alprazolam-Predicted	4.01	57.86	0.36
Alprazolam-Observed	3.70	66.34	0.46

Relative Infant Daily Dose (RIDD)

The IDD and RIDD were calculated by Simcyp software assuming the infant body weight of 3.5 kg and a daily milk intake of 0.150 L/Kg/day. The relative infant daily doses (RIDD) were found to be 10.56%, 6.51% and 3.98% for atenolol, alprazolam, and escitalopram, respectively.

Application of Lactation PBPK Model

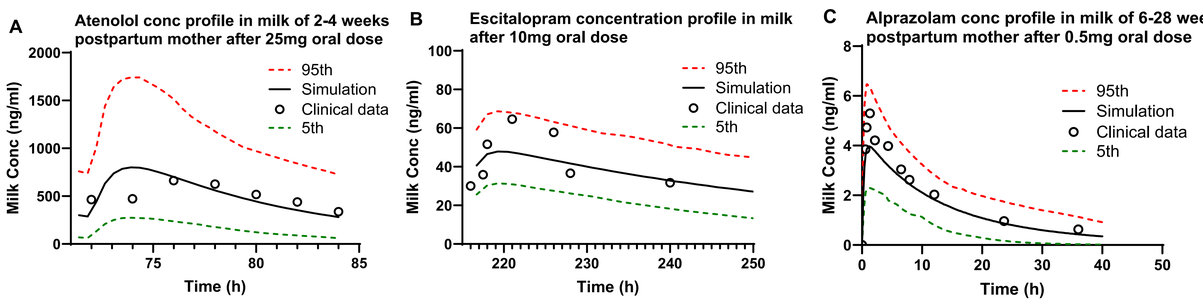

Fig.2. Atenolol[9] (A) and escitalopram[10] (B) concentration in milk at steady state, and alprazolam[11] (C) concentration in milk after single oral dose. Circles represent observed concentration in milk and solid black lines represent simulated concentration profile in milk. Red and green broken lines are 95th and 5th percentiles of simulated milk concentrations, respectively. Atenolol was given 25mg twice daily in 32 lactating mother of 2-4 weeks of postpartum. Escitalopram was given 10mg once a day in 3 lactating mother. The concentration of atenolol and escitalopram were measured at steady state. Alprazolam was given as a single oral dose of 0.50mg in 8 lactating mother of 6-28 weeks of postpartum.

Conclusion

- ❑ Current work shows the potential of lactation PBPK models to predict the drug exposure in human milk for 3 drugs that are not P-gp/BCRP substrates.
- ❑ A higher M/P ratio does not equate to a higher relative infant dose.
- ❑ Lactation PBPK models have potential to be used as a high-throughput screening tool for risk assessment in infants during the drug development process.
- ❑ The approach will be further evaluated for drugs that are substrates for active transporters known to be present in mammary tissues.

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