PREDICTION OF INFANT EXPOSURE TO MATERNAL DRUGS FROM BREAST MILK USING PBPK MODELING

Adeniyi Olagunju[1,2], Rajith KR Rajoli[1], Oluseye Bolaji[2], David Back[1], Saye Khoo[1], Andrew Owen[1], Marco Siccardi[1]
[1]University of Liverpool, Liverpool, UK; [2]Obafemi Awolowo University, Ile-Ife, Nigeria

Correspondence: olagunju@liv.ac.uk

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INTRODUCTION

- Therapeutic drug use during lactation is widespread despite lack of adequate information on breast milk excretion and the extent of breastfed infants' exposure for many drugs.
- Physiologically based pharmacokinetic (PBPK) models are increasingly being used in paediatric studies, with significant regulatory support.
- However, a cursory literature search indicates that its application in the study of infant exposure to xenobiotics through breast milk has been limited to environmental risk assessments.
- Recent advances in PBPK modeling now allow for integration of compartments and parameters representing the anatomical and physiological features of a nursing mother-infant pair (system parameters), with drug parameters to simulate complex scenarios of infant exposure to substances through lactation.

OBJECTIVES

- The aim of the present study was to develop and validate a bespoke PBPK model to predict infant exposure to maternal therapeutic drugs through breast milk for the first time.

METHODS

- The human breastfeeding model integrates a whole-body PBPK maternal model with a whole-body PBPK infant model. The model was built and simulated using SimBiology® module on MATLAB® (v5.1, MathWorks Inc., MA, USA).
- The infant sub-model was scaled from maternal model for different age groups (10 days-1, 1-3, 3-6, and 6-12 months) to account for age-dependent changes in system parameters.
- Modeling of processes regulating Absorption, Distribution, Metabolism and Elimination (ADME) was based on validated equations (**Table 1**)[1].
- In vitro data describing efavirenz (EFV) physicochemical properties, ADME, CYP expression, as well as induction, basic physiological and anatomical data were obtained from the literature.[2,3]
- Population variability in system and drug-specific parameters in both maternal and infant sub-models was introduced through anthropometric characteristics and MATLAB® rule expressions.
- Breastfeeding was described by four hourly oral doses of breast milk regulated by milk production/infant suckling rate. Suckling rate at 6 months was retained up to 12 months of age (mixed feeding).
- Virtual populations of nursing mothers taking 600 mg EFV daily and their breastfed infants (n = 100 per infant age group) were simulated.

Table 1 Key model equations used to describe ADME processes.

ADME Parameter	Equation
Fraction of dose absorbed (F_a)	$1-(1+\ 0.54\ x\ P_{eff})^{-7}$
Effective permeability (P_{eff})	$10^{(0.6836\ x\ (\log Caco-2))-0.5579)}$
Intestinal drug clearance (CL_{gut})	$(R\ x\ (CYP3A4\ rCL_{int}/0.34)\ x\ Ab_{CYP3A4}\ x\ 1000\ x\ 60)/10^6$
Drug escaping gut metabolism (F_g)	$\frac{Q_{gut}}{(Q_{gut}+ f_{u,gut}\ x\ CL_{gut}}$
Volume of distribution (V_{ss})	$(\sum_t V * P_{t:p}) + (V_e * E:P) + V_p$
Mass of microsomal protein per gram of liver (MMPGL)	$10^{(1.407+0.0158\ x\ Age-0.00038\ x\ Age^2+\ 0.0000024\ x\ Age^3)}$
Intrinsic clearance (CL_{int})	$(Ind\ x\ (rCL_{int}/0.34)\ x\ Ab_{CYP}\ x\ Ab_{CYP}\ x\ MMPGL\ x\ 1000\ x\ 60\ x\ Wt_{liver}))/10^6$
CYP2B6 induction (Ind_{CYP2B6})	$1+(5.7\ x\ [EFV]_{plasma})/(0.252+[EFV]_{plasma})$
Total intrinsic clearance (TCL_{int})	$TCL_{int}=\ (CL_{int}\ x\ Ab_{CYP}\ x\ Wt_{liver}\ x\ MMPGL\ x\ 1000\ x\ 60)/10^6$
Total apparent clearance (CL_{app})	$CL_{app}=\sum_{n=1}^{n} TCL_{int}$
Systemic clearance (CL)	$CL=\frac{Q_{hv}\ x\ f_u\ x\ CL_{app}}{Q_h+CL_{app}\ x\ f_u}$
Fraction escaping first-pass metabolism (F_h)	$F_h=\ 1-\ CL/Q_{hv}$
EFV dose per feeding session (EFV $Dose_{milk}$)	$V_{milk}\ x\ [EFV]_{milk}$
EFV concentration in breast milk ($[EFV]_{milk}$)*	$M/P_{AUC_{0-24}}\ x\ [EFV]_{plasma}$

*The model allows for using either a clinically derived or a model-predicted M/PAUC ratio

Figure 1 Observed plasma (A) and breast milk (B) EFV data (open circles) and simulated concentration-time profiles (solid lines, median; dotted lines, range).

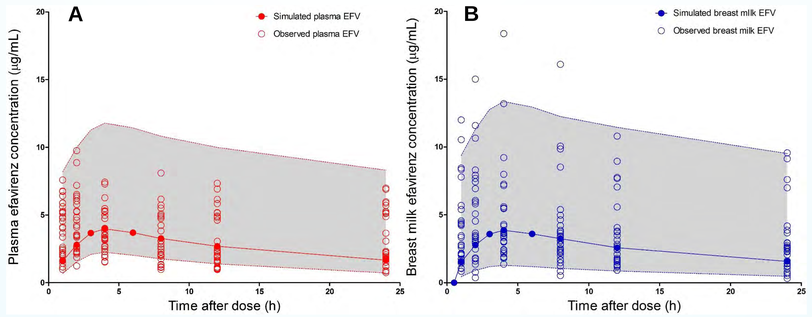
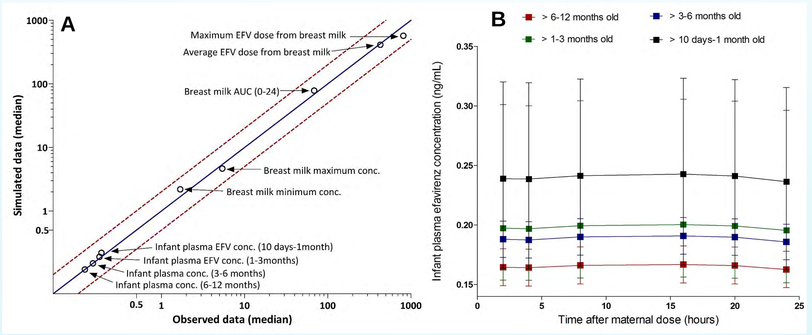


Figure 2 Simulated vs observed EFV breast milk PK parameters, infant exposure indices (A, red dotted lines represent 2-fold difference) and infant concentration-time profiles (B).



RESULTS

Table 2 Predicted vs observed PK parameters of EFV (median, range).

Parameters	Predicted (n = 400)	Observed (n = 29)[4]
Breast milk $AUC_{(0-24)}$ (µg.hr/mL)	78.2 (15.3-335)	68.5 (26.3-257)
Breast milk C_{max} (µg/mL)	4.65 (1.15-18.0)	5.39 (1.43-18.4)
Breast milk C_{min} (µg/mL)	2.19 (0.283-13.0)	1.68 (0.316-9.57)
Plasma $AUC_{(0-24)}$ (µg.hr/mL)	70.7 (21.0-336)	60.7 (26.8-177)
Plasma C_{max} (µg/mL)	4.26 (1.71-17.5)	4.63 (2.05-9.76)
Plasma C_{min} (µg/mL)	1.97 (0.371-12.6)	2.03 (0.755-6.74)
Average infant EFV dose from breast milk (µg/kg/day)	412 (82.3-2170)	428 (164-1610)
Maximum infant EFV dose from breast milk (µg/kg/day)	571 (131-2430)	809 (215-2760)
Infant plasma EFV conc., 10 days-1 month old (µg/mL)	0.22 (0.061-0.77)	0.19 (0.071-0.705)
Infant plasma EFV conc., 1-3 months old (µg/mL)	0.19 (0.037-0.81)	0.18 (0.036-0.504)
Infant plasma EFV conc., 3-6 months old (µg/mL)	0.15 (0.035-0.52)	0.15 (0.052-0.33)
Infant plasma EFV conc., 6-12 months old (µg/mL)	0.12 (0.026-0.60)	0.12 (0.038-0.590)

- Predicted anatomical and physiological parameters were within 50% difference of available data for all age groups (data not shown).
- The model adequately described EFV PK in plasma and breast milk, with over 90% of all individual (n = 29) observed data points within the predictive interval (**Figure 1**).[4]
- Predicted breast milk, plasma PK parameters and infant exposure indices were comparable to clinical data (**Figure 2A**; **Table 2**).[4]
- The resulting simulated concentration-time profiles in infants of different age groups were relatively flat (**Figure 2B**).
- A previously described model[5] was successfully integrated for M/P ratio prediction with a value of 0.83 for EFV.

DISCUSSION

- This approach adequately described infant exposure to EFV from breast milk, demonstrating the robustness of age-related changes in model parameters and the associated scaling and variability.
- The model can be used for other drug classes and in other therapeutic areas, provided the requisite drug-specific parameters are available or predictable from other known parameters.
- This application of PBPK modeling opens up opportunities for expanding our understanding of infant exposure to maternal drugs through breast milk, paving the way for evidence-based recommendations for drug use during lactation.

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