PERSPECTIVE

Addressing drug safety of maternal therapy during breastfeeding using physiologically-based pharmacokinetic modeling

INTRODUCTION

Breastfeeding can have positive health consequences for both the breastfed infant and the nursing mother. However, when taking medication, there are concerns about protecting the infant from adverse events while allowing necessary maternal therapy. An adverse effect on a breastfeeding infant due to maternal medication may be caused by an interplay of factors between the mother and the nursing infant, a complex scenario that can be readily investigated using physiologically-based pharmacokinetic (PBPK) modeling.

Multiple factors, including genetic and environmental, contribute to the variability associated with an individual's response. Exposure of mothers, particularly those with certain genotypes, to multiple medications during pregnancy and breastfeeding may place their infants at increased risk of adverse drug reactions. Consideration should also be given to the infant's smaller mass and immature gastrointestinal, hepatic, and renal function. Indeed, at this age, neonatal drug-excretory mechanisms, both hepatic and renal, are incompletely developed. Drugs chronically administered at that time through breastfeeding may accumulate and reach toxic concentrations.

PBPK models which account for the complex interplay between physiological parameters and drug-related characteristics, represent a mechanistic approach to predict the pharmacokinetics (PKs) of drugs in different populations, including nursing mothers[1] and infants.[2] Pediatric PBPK models account for the development of organs, including the ontogeny of specific enzymes and transporters involved in the disposition of a specific drug. Although knowledge gaps remain, ongoing research relating to these processes in children, has allowed refinement of relevant physiological parameters and integration of more complex models. Thus, PBPK models which are increasingly used in pediatric clinical pharmacology, including

drug development, are reaching maturation for applications with high regulatory impact.[2] In this paper, we discuss how "off the shelf" PBPK models for commonly used drugs, already robustly verified in terms of their disposition, can be used to assess safety concerns in breastfeeding infants as a consequence of the nursing mothers taking medication(s). Complex case studies will be used to demonstrate the validity of the approach.

CLINICAL LACTATION STUDIES IN DRUG DEVELOPMENT

In 2019, the US Food and Drug Administration (FDA) released a guidance document for pharmaceutical companies providing recommendations on how to address the potential impact of maternal drug exposure, including assessment of levels of the drug (and metabolite) appearing in breast milk, the potential effects on breastfeeding infants, and effects of the drug on milk production.[3] The FDA indicate that data from clinical lactation studies, supported by other relevant data, including drug physicochemical properties, mechanism of drug entry into breast milk, data from nonclinical studies, and infant factors, can be used to evaluate the safety of a drug when used by breastfeeding mothers and to develop recommendations to minimize infant exposure.

Key factors affecting the excretion of drugs into milk and methods of measuring the passage of drugs into breast milk have been described previously.[4] The standard method of quantifying drug passage into breast milk is the administration of a drug to a nursing mother, either for the purpose of the study or because she is taking the drug therapeutically. Ideally, sufficient drug concentrations are measured to allow calculation of an area under the milk concentration–time curve (AUC) and an average milk concentration (AUC/milk sampling duration).

Once an estimate of drug concentration in milk is available, an infant daily dose assuming a daily milk intake of 150 ml/kg and a milk/plasma ratio can be calculated. Thereafter, the relative infant daily dose (RIDD; the percent of the weight-adjusted maternal dosage consumed in breast milk over 24 h) is determined. The World Health Organization (WHO) Working Group proposed that drugs with an RIDD >10% may not be safe in infants, and that those with an RIDD greater than 25% should be avoided in nursing mothers.

PREDICTING DRUG CONCENTRATIONS IN MILK

The amount of drug excreted into breast milk depends upon the composition of the milk, the physicochemical properties of the drug, and the mechanism of transport. The higher the lipid solubility, the greater the concentration in human milk. The majority of drugs appear to be transported into mammary blood capillaries via passive diffusion. In the absence of clinical lactation data, it may be possible to predict the passage of drugs into breast milk (M/P ratio) using only the physicochemical properties of the drug and milk characteristics. Indeed, a number of such predictive algorithms have been developed and evaluated.[4,5]

Integration of these M/P ratio prediction algorithms within a PBPK model can facilitate simulation of drug levels in breast milk following administration of the drug in mothers.[1] Thereafter, the infant daily dose and RIDD of a drug based on ingestion via breast milk can be predicted from the simulated milk concentration profiles and used to guide neonatal/infant risk assessment where clinical lactation data are lacking. In the context of regulatory application, "well-qualified models" are required to provide assurances that the model predictions are robust and this approach can be used to inform with confidence, high-impact decisions as part of regulatory submissions.[6] Although it is accepted that this is an emerging and significant area of interest, evaluation of such approaches is already ongoing and results are promising.[1,4]

PREDICTING DRUG CONCENTRATIONS IN INFANTS DURING BREASTFEEDING

When clinical lactation data are available, some of the uncertainty associated with extrapolation of the infant daily dose is removed. Here, we present two case studies where observed milk concentrations were available and the extrapolated infant daily dose was used to simulate plasma concentration time profiles in infants using a pediatric PBPK model (Johnson et al.[2]); one involves a drug–drug interaction for a combination therapy, and the other, the complex interplay between mother/infant and the impact of their respective CYP2B6 genotypes.

Case study 1: Lumacaftor/ivacaftor

Cystic fibrosis (CF) is a life-shortening genetic disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. These mutations lead to abnormal ion transport in mucous membranes throughout the body, including the respiratory tract. As a consequence of CFTR modulator therapy, there has been a significant increase in the quality of life for those with CF. Pregnancy was once discouraged for women with CF but now, even with moderately severe lung disease, women can successfully navigate pregnancy. However, with the increasing use of this medication, there is a growing need to understand the effects of these agents during pregnancy. The uncomplicated and successful pregnancy of a woman treated with lumacaftor/ ivacaftor, as well as the clinical course of the infant during the first 9 months of life, was reported recently.[7] Concentrations of lumacaftor and ivacaftor in maternal plasma, cord blood, breast milk, and infant plasma over time were recorded throughout.

A PBPK model describing the ivacaftor/lumacaftor combination that was able to capture the induction of CYP3A4-mediated metabolism of ivacaftor by lumacaftor for a number of different dosage regimens, was reported previously.[8] In the case study presented here, the published PBPK models were used to predict the exposure of both drugs in breastfeeding infants during their first 9 months of life, thus replicating the clinical scenario.[7] Virtual neonates with time-varying physiology, including a CYP3A4 ontogeny, were generated and given an infant daily dose of each drug (extrapolated from the observed milk data). As milk intake via breast-feeding was not constant, various scenarios were assessed (25% of dietary intake from breast milk up to 100%; Figure 1). Although data from only a single infant were available for comparison, the results are promising especially when considering the complexity of the situation.

Case study 2: efavirenz

Current WHO guidelines recommend efavirenz as the preferred non-nucleoside reverse transcriptase inhibitor component of first-line antiretroviral therapy for adults across different patient populations, including nursing mothers. However, efavirenz is not licensed for use in
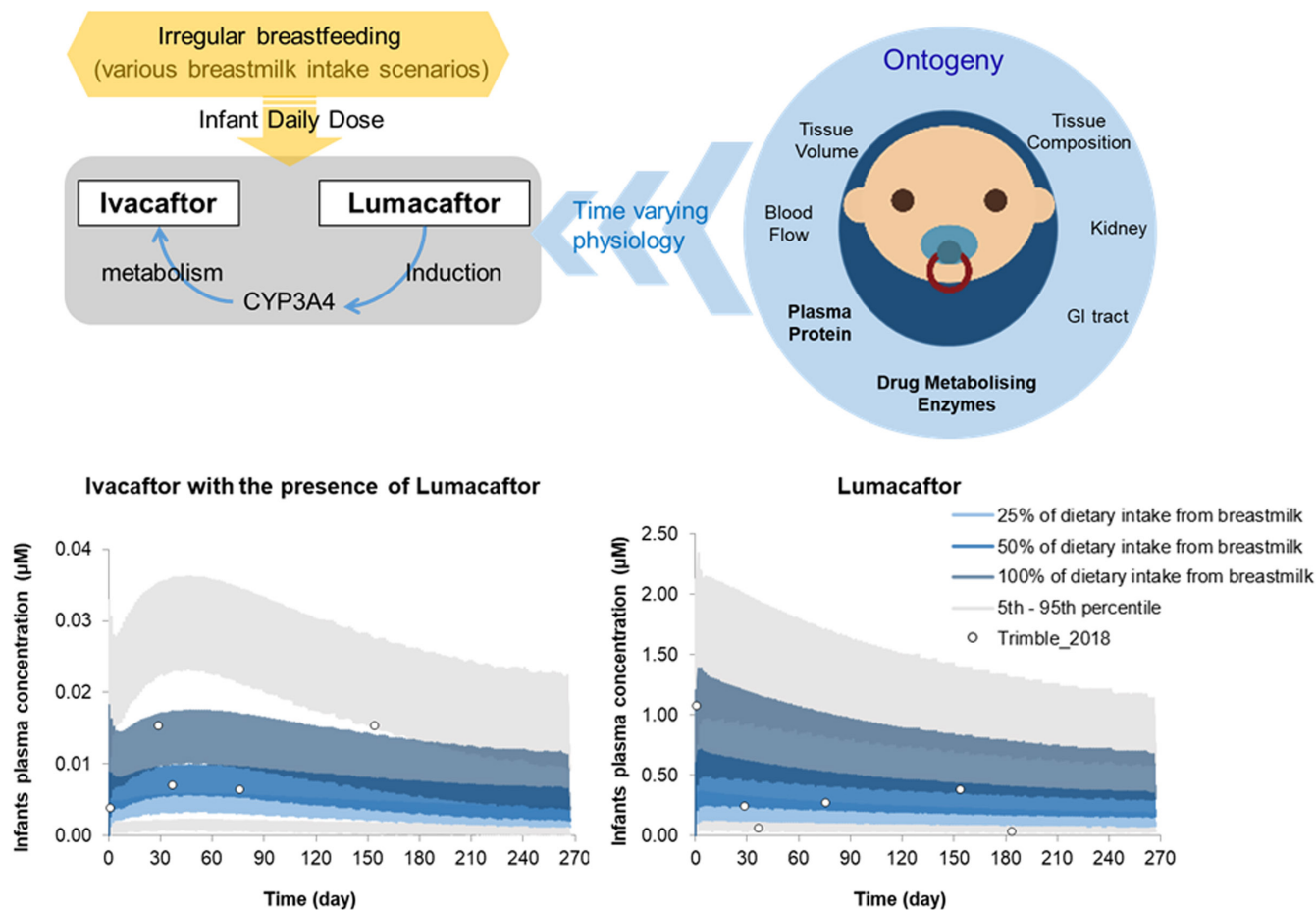
FIGURE 1 Ivacaftor and lumacaftor case study. (Top) The schematic illustrates key factors considered in the PBPK model for predicting ivacaftor and lumacaftor exposure in infants during breastfeeding. (Bottom) Simulated and observed concentration–time profiles of ivacaftor and lumacaftor in newborn girls being breastfed for 184 days. All simulations were performed using the population-based Simulator (Simcyp version 21; Sheffield, UK). Blue lines represent simulated mean profiles following various breast milk intake scenarios. Gray lines represent the 5th and 95th percentile of the total virtual population (Sim-Pediatric, 100 female subjects at birth per each scenario). Open circles represent observed data in a full-term newborn girl.[7] GI, gastrointestinal; PBPK, physiologically-based pharmacokinetic

children <3 months old or weight ≤3.5 kg because optimal dosing and safety have not been evaluated. Despite this, the drug is widely used by nursing mothers. An observational study was conducted to investigate maternal plasma and breast milk PKs of efavirenz and breastfed infants' exposure in genetically defined subgroups of HIV positive nursing mothers.[9] Potential variability due to genetic polymorphisms in CYP2B6, NR1I3, CYP2A6, ABCB1, ABCB5, and ABCG2 was evaluated. CYP2B6 516G>T was independently associated with efavirenz concentrations in maternal plasma, breast milk and infant plasma ($n = 134$). When stratified according to CYP2B6 516G>T genotypes ($n = 29$; 11 GG, 10 GT, and 8 TT), efavirenz PK parameters in plasma and breast milk differed significantly between patient groups. No efavirenz-related toxicity was reported and the RIDD was reported to be <10% in most breastfed infants.

A robust PBPK model for efavirenz describing the CYP3A4- and CYP2B6-mediated auto-induction during multiple dosing was reported previously.[10] In the case study presented here, the published PBPK model was used to predict the exposure of efavirenz in maternal and infant plasma accounting for the various CYP2B6 genotypes. Virtual infants with time-varying physiology, including a CYP2B6 ontogeny, were generated. The infant daily doses were estimated based on the clinically observed M/P ratio of 1.1 and efavirenz exposures in mothers carrying different CYP2B6 genotypes. The clinically significant trend toward higher infant efavirenz exposure from GG/GG to TT/TT composite maternal/infant CYP2B6 genotypes was captured reasonably well by the PBPK model (Figure 2).

Concluding remarks

Most drug labels do not provide enough information to guide a woman and her physician in deciding whether a
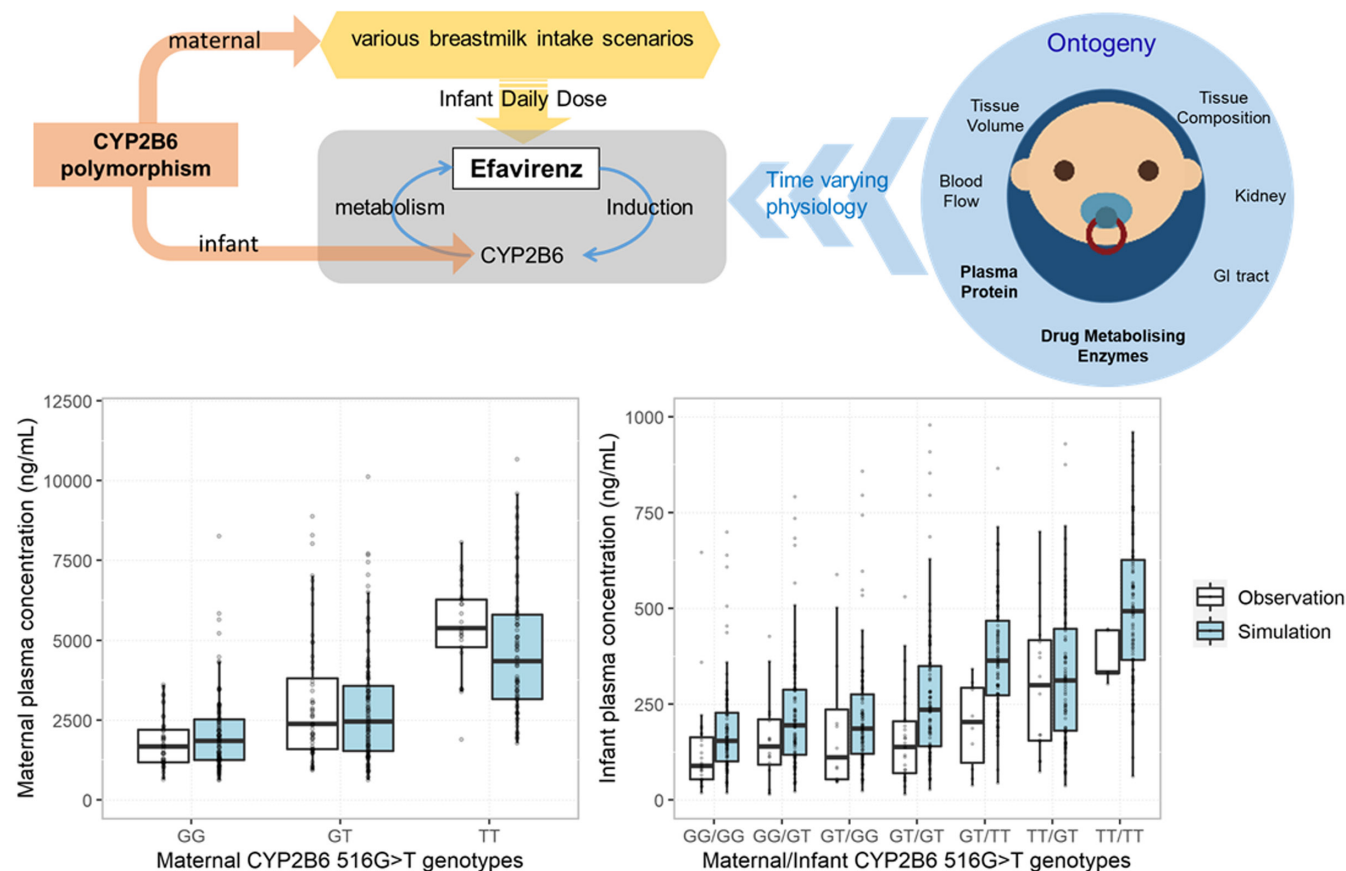
FIGURE 2 Efavirenz case study. (Top) The schematic illustrates key factors considered in the PBPK model for predicting the impact of CYP2B6 polymorphism on efavirenz exposure in infants during breastfeeding. (Bottom left) Simulated and observed efavirenz plasma concentrations (data points) in mothers carrying various CYP2B6 516G>T genotypes; (bottom right) simulated and observed infant efavirenz plasma concentrations (data points) associated with composite maternal/infant CYP2B6 516G>T genotypes. The observed maternal (age: 18–44 years) and infant (age: 0.29–75 weeks, 52% girls) data were from Olagunju et al.[9] The simulations were performed in 100 virtual female adults or pediatrics per each CYP2B6 genotypes (Sim-Healthy volunteers, 18–44 years old; Sim-Pediatric, 0.29–75 weeks old, 52% girls). GI, gastrointestinal; PBPK, physiologically-based pharmacokinetic

medication is safe during breastfeeding. PBPK modeling can be used to predict drug exposures in both mothers and infants while accounting for complex factors, such as genetics, comedications, and time-varying physiology. Robust "off the shelf" PBPK models that have been extensively verified with supporting clinical data are already available for many commonly prescribed drugs. Along with other methods, this approach can be used to support benefit–risk decisions for both the nursing mother and the breastfeeding infant in early drug development and through practice.

CONFLICT OF INTEREST

K.R.Y. and X.P. are employees of Certara UK Limited (Simcyp Division) and may hold shares in Certara. As an Associate Editor for Clinical Pharmacology & Therapeutics: Pharmacometrics & Systems Pharmacology, K.R.Y. was not involved in the review or decision process for this paper.

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