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Development of a Generic Physiologically Based Pharmacokinetic Model for Lactation and Prediction of Maternal and Infant Exposure to Ondansetron via Breast Milk

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Abstract

Ondansetron is commonly used in breastfeeding mothers to treat nausea and vomiting. There is limited information in humans regarding safety of ondansetron exposure to nursing infants and no adequate study looking at ondansetron pharmacokinetics during lactation. We developed a generic physiologically based pharmacokinetic lactation model for small molecule drugs and applied this model to predict ondansetron transfer into breast milk and characterize infant exposure. Drug-specific model inputs were parameterized using data from the literature. Population-specific

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7.Author Contributions

KW, JC, CF, KH, CH, SB, and KZ designed the research. SP, GS, DH, BH, and PB enrolled participants in the prospective study and contributed to the manuscript. KMJ, KW, JC, and AD analyzed the data and wrote the manuscript.

10.Supplementary Material

Two documents supplement this work: 1) Supplement I—Model development and evaluation, calculated milk-to-plasma ratio, postpartum parameters sensitivity analyses, and individual concentration-time curves and 2) Supplement II—Implementing the lactation PBPK model for a new compound.

Conflict of Interest: Dr. André Dallmann is an employee of Bayer AG and uses Open Systems Pharmacology software, tools, and models in his professional role. All other authors declared no competing interests for this work.

inputs were derived from a previously conducted systematic literature review of anatomic and physiologic changes in postpartum women. Model predictions were evaluated using ondansetron plasma and breast milk concentration data collected prospectively from 78 women in the Commonly Used Drugs During Lactation and infant Exposure (CUDDLE) study. The final model predicted breast milk and plasma exposures following a single 4 mg dose of intravenous ondansetron in 1000 simulated women who were two days postpartum. Model predictions showed good agreement with observed data. Breast milk median prediction error (MPE) was 18.4% and median absolute prediction error (MAPE) was 53.0%. Plasma MPE was 32.5% and MAPE was 43.2%. The model-predicted daily and relative infant doses were 0.005 mg/kg/day and 3.0%, respectively. This model adequately predicted ondansetron passage into breast milk. The calculated low relative infant dose indicates that mothers receiving ondansetron can safely breastfeed. The model building blocks and population database are open-source and can be adapted to other drugs.

Keywords

ondansetron; physiological based pharmacokinetic model; lactation; postpartum

1. Introduction

One of the potential barriers to breastfeeding is maternal use of prescription and over-the-counter drugs and the perceived risk to the baby from drug passage into breast milk.[1,2] Between 50–80% of lactating women take at least one prescription medication while breastfeeding.[3–6] For most drugs, the extent of transfer into breast milk is either unknown or limited to case reports or small case series.[7–9] A recent review of the LactMed database showed that fewer than 2% of the thousands of medications currently marketed in the U.S. have sufficient human data supporting safety while breastfeeding.[10] As a result of this uncertainty, many women and their medical providers struggle with the decision to either avoid taking necessary medications or discontinue breastfeeding.[11–14]

Determining the extent of drug transfer into breast milk is challenging with traditional pharmacokinetic (PK) trials. Anatomic and physiologic changes occurring after delivery require the enrollment of large numbers of lactating women throughout the postpartum period. This challenge can be overcome by using sophisticated physiologically based pharmacokinetic (PBPK) modeling. PBPK models are a complex set of mathematical equations of interconnected virtual organs that incorporate physiology with drug physicochemical properties to describe drug disposition. PBPK modeling and simulation can be used to leverage available data. These techniques have already been used to describe drug PK in pregnant women.[15] Ondansetron is commonly used in breastfeeding mothers to treat nausea and vomiting. Animal studies suggest that ondansetron is present in breast milk[16], but there are no human data about the extent of ondansetron transfer into human breast milk and no quantitative data describing infant exposure. The goals of this study were to develop a generic lactation PBPK model for small molecule drugs (molecular weight < 900 g/mol) and to apply this model to ondansetron to predict ondansetron exposure in breast milk. We adapted an existing pregnancy PBPK model[17] to the postpartum period and then

evaluated model predictions using prospective, observed data from lactating women enrolled in the Pediatric Trials Network sponsored Commonly Used Drugs During Lactation and infant Exposure (CUDDLE) study.

2. Material and Methods

2.1 Software

The lactation PBPK model was developed using PK-Sim and MoBi, available as freeware under the GNU General Public License version 2 (GPLv2) license through Open Systems Pharmacology (version 9.1, http://www.open-systems-pharmacology.org/). The software R (version 3.6.3, R Foundation for Statistical Computing, http://www.r-project.org) and SQLite Expert (Professional Edition, http://www.sqliteexpert.com/) were used to create a virtual population of lactating women. Analyses and plot creation were carried out in PK-Sim, R, and STATA (version 16.0). WebPlotDigitizer (version 4.4) was used for data extraction from published literature.

2.2 General Workflow

The lactation PBPK model was developed in two steps: 1) creation of the PBPK structure in MoBi and 2) creation of a postpartum population (Figure 1). The PBPK structure was adapted from a previously published pregnancy PBPK model for ondansetron.[17] In order to adapt the pregnancy model, we first removed the pregnancy-specific compartments and modified the breast compartment by adding a milk sub-compartment. Anatomic and physiologic parameters in the postpartum population were scaled based on a recent meta-analysis of changes during the postpartum period.[18] We included estimates of inter-individual variability in model parameters (e.g., organ weights, blood flows, intrinsic clearance) to simulate population-level data. The model was evaluated by comparing model predictions with prospectively collected in vivo data from lactating women who were taking ondansetron.

2.3 Development of Ondansetron PBPK Lactation Model

2.3.1 Ondansetron—Ondansetron is a selective 5-HT_3 receptor antagonist with a bioavailability of 56–60% and protein binding of 70–76%. Albumin is the major plasma protein that binds ondansetron.[19] The volume of distribution at steady-state (Vss) is 1.7–2.3 L/kg in nonpregnant women and 1.5–2.1 L/kg in pregnant women.[20] Ondansetron is extensively metabolized by cytochrome P450 (CYP) 3A4, CYP1A2, and CYP2D6 with only 5% of drug remaining unchanged in urine. Metabolites are not active.[21] In healthy men and women, clearance has been calculated at 0.26–0.38 L/h/kg;[21] in pregnant women, clearance is comparable at 0.19–0.27 L/h/kg.[20] Ondansetron half-life is 3.5–5.5 h in adults and 5.4 h in pregnant women.[16,19–21] Physicochemical properties of ondansetron used in the PBPK model are included in Table 1.

2.3.2 Lactation Model Structure—As noted above, the lactation PBPK model structure was based on a previously published PBPK model for pregnant women.[17] Pregnancy-specific compartments (i.e., placenta, amniotic fluid, fetus, and cord blood compartments) were removed from the structural model, along with all neighborhood

connections to the arterial and venous blood pools (Figure 2A). In addition, a milk sub-compartment was added to the breast compartment (Figure 2B). The model assumes that drug passage into the milk only occurs via passive diffusion from the plasma sub-compartment. Breast and lactation parameter values were parameterized based on a systematic search of the literature. If no quantitative information was available, physiologically plausible assumptions were made based on physiochemical properties of ondansetron.

2.3.3 Search Terms—The following terms were used for searching literature: ((‘pregnan*’, ‘trimester’, ‘gestation’, ‘antenat*’, ‘prenat*’, ‘perinat*’, ‘peripart*’, ‘postpart*’, ‘postnat*’, ‘parturition’) AND (‘*milk’, ‘colostrum’, ‘lact*’)) AND (‘passage’, ‘plasma’).

2.3.4 Parameterization of Transfer of Ondansetron into Breast Milk—The differential equation for change in molar drug amount in the milk sub-compartment is shown in Eq. 1:

$$\frac{dN_{milk}}{dt} = P_{plasma \rightarrow milk} \bullet SA_{plasma,milk} \bullet f_u \bullet C_{plasma} - P_{milk \rightarrow plasma} \bullet SA_{plasma,milk} \bullet f_u \bullet \frac{C_{milk}}{K_{milk:plasma}} \quad \text{Eq. 1}$$

where N_{milk} denotes the molar drug amount (μmol); $P_{plasma \rightarrow milk}$ and $P_{milk \rightarrow plasma}$ refers to the permeability (cm/min) from plasma to milk and milk to plasma, respectively; $SA_{plasma,milk}$ indicates the surface area between plasma and milk across which the drug diffuses (cm^2); f_u represents the fraction unbound of the drug in plasma; C_{plasma} and C_{milk} are the molar drug concentrations (μmol/L) in plasma and milk, respectively; and $K_{milk:plasma}$ is the milk-to-plasma partition coefficient at steady state.

2.3.4.1 Permeability: Ondansetron is a small molecule that is lipophilic and weakly basic. As a result, the permeability from plasma to milk ($P_{plasma \rightarrow milk}$) and milk to plasma ($P_{milk \rightarrow plasma}$) were assumed to be equal and instantaneous.[22] Therefore, $P_{plasma \rightarrow milk}$ and $P_{milk \rightarrow plasma}$ were set to 100 cm/min for the model, a value which is similar to the permeability in the other organ compartments with instantaneous drug exchange.

2.3.4.2 Surface Area: The surface area of the plasma to milk barrier was assumed to be a function of the total surface area of the breast acini found in both breasts.

Each acinus was assumed to be ellipsoidal. Data for the radial axes of the alveoli were extracted from Mortazavi et al [23] (arithmetic mean ± standard deviation): long axis radius = 71.62 ± 58.17 μm; short axis radius = 44.90 ± 27.89 μm. Individual acini surface area was calculated based on the formula for a prolate ellipsoid described by Cotes[24,25] (Eq. 2):

$$Surface\ Area\ (\mu m^2) = 2\pi b\left(a \bullet \frac{arcsin\sqrt{q}}{\sqrt{q}} + b\right) \quad \text{Eq. 2}$$

where a and b are the radial axes (μm), $a > b$, and $q = 1 - \frac{b^2}{a^2}$.

Data for the number of acini per lobule were extracted from Jindal et al [26]: 107.96 ± 224.22 secretory acini per lobule (arithmetic mean ± standard deviation).

The number of lobules per lobe was based on maternal age. Data for this calculation was extracted from Figueroa et al [27] and a polynomial function was fitted to the data (Eq. 3):

$$\textit{Number of lobules per lobe} = \left(-5 \times 10^{-7}\right)x^4 + \left(4 \times 10^{-5}\right)x^3 + 0.0011x^2 + 0.2687x + 11.861 \quad \text{Eq. 3}$$

where x is the postpartum woman's age in years. A 31-year-old, lactating woman was thus assumed to have an average of 5.32 lobules/lobe.

Ramsay et al[28] found an average of 9.6 ± 2.9 and 9.2 ± 2.9 (arithmetic mean ± standard deviation) lobes per left and right breast, respectively. The surface area calculation therefore assumed an average total of 18.8 ± 4.1 lobes for both breasts.

The average total surface area of the milk to plasma barrier, $SA_{plasma,milk}$, was assigned an initial value of 3.87 cm^2 for a 31-year-old, lactating woman. Of note, as the permeability was assumed to be very high because of instantaneous drug exchange, the value of $SA_{plasma,milk}$ was insensitive in the model because drug distribution into the milk was blood-flow limited rather than permeability-limited.

2.3.4.3 Volume of Milk: The volume in the milk is a function of milk consumption by the infant. Infant consumption increases as the infant ages and correlates with infant weight. The volume of milk produced per day in mL was calculated by multiplying the baby weight-normalized formula described by Yeung et al[29] by the calculated baby weight (Eq. 4) and the reported milk remaining after breastfeeding.

$$V_{milk}\left(mL/day\right) = \theta_1 \bullet \frac{\theta_2}{\theta_2 - \theta_3} \bullet \left(e^{-\theta_3 t} - e^{-\theta_2 t}\right) \bullet W_{baby} \bullet (1 - V_{exp}) \quad \text{Eq. 4}$$

where V_{milk} was the milk volume (mL); θ_1, θ_2, and θ_3 were fitted parameters, 160.39, 0.232, and 0.00252, respectively; t was the time after delivery in days; V_{exp} was the fraction of milk expressed per feeding (0.57 ± 0.38, mean ± standard deviation) in mL[30]; and W_{baby} was the calculated weight of the baby (kg).

The weight of the baby was dependent on sex and time after birth. W_{baby} was assigned based on the 50th percentile described in the World Health Organization baby growth charts during the first two years of life.[31] Data for boys (Eq. 5) and girls (Eq. 6) were extracted and a polynomial function was fitted to the data.

$$W_{baby\_boy}(kg) = \left(-1 \times 10^{-4}\right)t^4 + (0.006)t^3 - 0.1316t^2 + 1.4659t + 2.0218 \quad \text{Eq. 5}$$

$$W_{baby\_girl}(kg) = \left(-8 \times 10^{-5}\right)t^4 + (0.0047)t^3 - 0.1048t^2 + 1.2448t + 1.948 \quad \text{Eq. 6}$$

where t was the time after delivery in weeks.

Organ volume for breasts, as described by Dallmann et al[18], was assumed to include milk volume for one feeding. Therefore, the volume of the milk sub-compartment was assumed to be $\frac{V_{milk}}{n}$ where n was the number of feedings per day. For this model, a mean [range] of 7.7 [4.3, 13.8] feedings was assumed per day with infants being exclusively breastfed.[29]

2.3.4.4 Milk to Plasma Partition Coefficient: The milk-to-plasma concentration ratio for total ondansetron was initially estimated using ondansetron's physiochemical properties (see Table 1) and followed procedures according to the method described in Larson et al.[32,33] This method assumes exclusive passive diffusion and rapid equilibrium and uses the pKa values, the octanol/water partition coefficient (logP), and the protein binding of a drug as input variables. For basic drugs, such as ondansetron (pKa [basic]: 7.8), the model equation is shown below (Eq. 7):

$$ln\left(M/P\right) = -0.09 + 2.54\ ln\left(Mu/Pu\right) + 0.8\ ln(f_u) + 0.46\ lnK \quad \text{Eq. 7}$$

where M/P is the milk-to-plasma concentration ratio of the total drug, Mu/Pu is the unbound milk to plasma ratio defined by Eq. 8, f_u is the unbound fraction of drug in plasma, and K is defined in Eq. 9.

$$Mu/Pu = \frac{1 + 10^{pKa - pHmilk}}{1 + 10^{pKa - pHplasma}} \quad \text{Eq. 8}$$

where the plasma pH ($pHplasma$) is assumed to be 7.4 and the pH of milk ($pHmilk$) varies by time in the postpartum period. [34] Colostrum pH is approximately 7.45; breast milk pH ranges from 7.0 and 7.1 until 3 months postpartum and increases to 7.4 by 10 months. The transition between colostrum to milk was set as 3 days. The three-month transition was set as 12 weeks. The calculated milk-to-plasma ratios are provided in Supplement I (Table S1)

$$K = log\left(\frac{0.955}{f_{u,milk}}\right) + (0.045 \bullet L_{milk}) \quad \text{Eq. 9}$$

$$f_{u,milk} = \frac{f_u^{0.45}}{\left(6.94\ x\ 10^{-4}\right) + f_u^{0.45}} \quad \text{Eq. 10}$$

$$\log L_{milk} = 1.29 log\ p - 0.88 \quad \text{Eq. 11}$$

where $f_{u,milk}$ (Eq. 10) is the fraction unbound of drug in milk and L_{milk} (Eq. 11) is the logarithm of the octanol/water partition coefficient.

For model building, the milk to plasma partition coefficient ($K_{milk:plasma}$) was defined as the ratio between the milk and plasma compartments at equilibrium (M/P). For the structural model developed in MoBi, $K_{milk,\ unbound:plasma,\ unbound}$ and $f_{u,milk}$ were described as follows (Eq. 12):

$$K_{milk:plasma} = K_{milk,unbound:plasma,unbound} \bullet \frac{f_u}{f_{u,milk}} \quad \text{Eq. 12}$$

Paired milk and plasma in vivo concentration data from the prospective CUDDLE study were compared to the different calculations for $K_{milk:plasma}$.

2.3.5 Clearance—CYP3A4, CYP1A2 and CYP2D6 were assumed to contribute equally to metabolism.[17] While CYP activity has been documented to change during pregnancy, data are sparse on what occurs immediately after delivery. The majority of CYP activity data are obtained 6–8 weeks postpartum and show a return to baseline of CYP activity by that time. Because we focused on the first week postpartum, our model initially assumed that intrinsic clearance for each CYP was the same as late in the 3rd trimester of pregnancy. However, CYP expression is known to revert to pre-pregnancy levels in the postpartum period, though the rate is unknown.[17,20,35]

2.4 Development of a Postpartum Population

A virtual postpartum population was developed for use in simulations. Briefly, organ volumes, organ flows, glomerular filtration rate, and organism specific parameters were compiled in R as a function of time after delivery in weeks based on previously described postpartum formulas compiled from literature (See Supplement I Table S2).[18] The resulting parameter data frame was added to the physiologic SQL database file found in the portable version of PK-Sim using SQLite Expert Professional software. The updated SQL file was then imported into the portable version of PK-Sim for implementation and simulation.

2.5 Observed Data for Evaluation of PBPK Model Predictions

2.5.1 Sample Collection—Pharmacokinetic (PK) samples were collected from the Pediatric Trials Network sponsored CUDDLE study (NCT03511118). This is an active, open-label, multicenter study collecting PK and safety data for ondansetron and 30 other understudied drugs administered to lactating women as part of their standard of care. Lactating women who received at least one drug of interest up to 180 days postpartum and their maternally breastfed infants up to 180 days of age were eligible for enrollment. Exclusion criteria included known pregnancy during the PK sampling period and any concomitant condition that the site principal investigator or physician providing care felt would preclude participation in the study. The study was approved by all participant site ethical review committees and all participants signed informed consent.

2.5.2 Drug Dosing and Sample Collection—Ondansetron was given per standard of care. Dosing information was collected for up to 8 doses prior to the sampling dose. Lactating women could choose to have samples collected from maternal breast milk, maternal blood, and/or breastfed infant blood. Sampling was guided by optimal PK sampling points; however, samples collected outside those windows were allowed. Blood samples

were collected during routine lab draws whenever feasible. Maternal breast milk samples were collected at times convenient for the mothers.

2.5.3 Analytical Methods—Maternal blood was collected (3 mL) in an EDTA-K2 Microtainer and processed for plasma PK samples immediately prior to freezing at −70°C. Breast milk was collected (2–4 mL) in a single-use cryovial and was placed immediately in −70°C freezer or −20°C freezer if −70°C freezer was not immediately available and transferred to a −70°C within one hour. Samples were sent to the PTN central laboratory (Frontage Lab, Exton, PA, US) for storage and analysis. Ondansetron concentrations were quantified using validated liquid chromatography-tandem spectrometry assay. For both assays, the method was linear ($R^2 \geq 0.98$) over the range of 0.0500 ng/mL to 50.0 ng/mL. The intra-run and inter-run precision and accuracy of the method met the FDA acceptance guidelines.[36] At each concentration level, the overall accuracy was within ± 15% of the nominal value (± 20% at the LLOQ) and the %CV was no more than 15% (20% at the LLOQ). Recovery was determined for ondansetron at three QC concentration levels. For each concentration, three measurements were performed. The variability (%CV) of the peak area ratio for each QC was ≤ 15%.

2.5.4 Exposure in Mothers and Breastfed Infants—The maternal milk/plasma (M/P) ratio was calculated by dividing the ondansetron breast milk concentration by the ondansetron maternal plasma concentration for concomitantly collected samples (+/−60 minutes).

In order to simulate exposure in breast milk and the breastfed infant, we used the final model to predict ondansetron exposure in breast milk and plasma. Based on FDA guidance, we estimated the daily infant dose (DID).[37] The DID estimates the quantity of drug delivered to an infant via breast milk in a given day as expressed in Eq 13.

$$Estimated\ Daily\ Infant\ Dose\left(\frac{\frac{mg}{kg}}{day}\right) = \sum C_{Milkave} x\ Milk\ volume \quad \text{Eq. 13}$$

The milk volume consumed was assumed to be 200 mL/kg/day based on FDA guidance for young infants.[37] $C_{Milkave}$ is the average milk concentration calculated according to Eq. 14.

$$C_{Milkave} = \frac{AUC_{inf}}{\tau} \quad \text{Eq. 14}$$

where AUC_{inf} is the area under the concentration time curve through infinity after dose 1 using the linear up/log down trapezoidal method; and τ is the dosing interval of 8 hours.

We then used the estimated DID to calculate relative infant dose (RID). The RID relates the potential dose of the drug delivered to the infant to the typical therapeutic dose. Based on FDA guidance we compared the estimated daily infant dose to the daily maternal dose using Eq. 15.[37]

$$RID_{I:M}(\%) = \frac{Estimated\ Daily\ Infant\ Dose\left(\frac{mg}{kg}{day}\right)}{Maternal\ dosage\left(\frac{mg}{kg}{day}\right)} x100 \quad \text{Eq. 15}$$

We used 12 mg/day to represent a "typical" daily dose of 4 mg every 8 hours, using the median maternal weight in the study.

Because ondansetron is administered to infants to treat nausea, we also compared the estimated DID to recommended infant dose of 0.1 mg/kg every 8 hours (0.3 mg/kg/day)[38] using Eq. 16.

$$RID_{I:I}\left(\%\right) = \frac{Estimated\ Daily\ Infant\ Dose\left(\frac{mg}{kg}{day}\right)}{Infant\ dosage\left(\frac{mg}{kg}{day}\right)} x100 \quad \text{Eq. 16}$$

2.6 Evaluation of PBPK Model Predictions

The lactation base model was used to generate concentration vs. time profiles to compare with observed data. Because no published studies of ondansetron passage into breast milk exist in current literature, we randomly split (50:50) the observed data from the CUDDLE study into development and validation datasets. Model parameters were optimized by comparing model predicted concentrations with the development data using Monte Carlo simulation in the PK Sim parameter identification toolbox. The optimized model was used to generate population predictions of plasma concentration vs. time profiles for a virtual population of lactating women (n = 1,000) using the postpartum population (Section 2.4) and compared to the validation data. Model predictions were visually evaluated in goodness-of-fit (GOF) and residual versus time plots, and numerically by median absolute prediction error (MAPE) and median prediction error (MPE).[39] Prediction error (PE) was defined by Eq. 17.

$$\boldsymbol{PE\left(\%\right) = \frac{C_{observed} - C_{simulated}}{C_{simulated}} x100} \quad \text{Eq. 17}$$

where $C_{observed}$ were measured concentrations and $C_{simulated}$ were simulated concentrations. MAPE and MPE were then defined by Eq. 18 and Eq. 19.

$$MAPE(\%) = \{\boldsymbol{median}\ |PE_{ij}|\ ,\ \boldsymbol{j = 1 \ldots N_i}\} \quad \text{Eq. 18}$$

$$MPE(\%) = \{\boldsymbol{median}\ PE_{ij},\ \boldsymbol{j = 1 \ldots N_i}\} \quad \text{Eq. 19}$$

where i refers to the individual and N_i is the number of performance errors in the i^{th} individual.

As a further check of the model, sensitivity analyses for model parameters were also performed.

2.7 Extending the Lactation PBPK Model to Other Drugs

The lactation model can be extended to other drugs. Lactation model building blocks and the SQL file with the postpartum population (PK-Sim physiological database) are available on GitHub (https://github.com/Open-Systems-Pharmacology). Passive transport and spatial structure building blocks can be imported into MoBi and used to construct new lactation simulations. Population simulations can be run in the portable version of PK-Sim through a two-step process that involves 1) replacing the SQL database in the PK-Sim folder and 2) exporting the MoBi simulation to PK-Sim. The workflow for extending this model to other drugs is similar to the previously described workflow for pregnant women [40] and is described for breastfeeding women further in the Supplement II.

3. Results

3.1 Observed Data from the CUDDLE Study

The CUDDLE study enrolled 80 lactating women receiving ondansetron. Maternal demographics are shown in Table 2. Two women who received enteral ondansetron were not included in this analysis. The 78 women included in the analysis contributed a total of 67 plasma samples and 54 breast milk samples. One breast milk sample was below the limit of quantitation and was not included in the analysis. Women contributed a median (range) of 1 (1, 2) plasma sample and 1 (1,5) milk sample. Nineteen participants had paired plasma-breast milk samples with a median (range) M/P ratio of 0.86 (0.34, 1.88). The observed M/P ratio was slightly less than the calculated M/P ratio, which was 0.95. Fifty-five women received a single 4 mg dose of IV ondansetron prior to PK sampling and 23 received multiple doses. Among the women who received multiple doses, one received a 4 mg dose followed by an 8 mg dose, and one received two 8 mg doses. The median (range) time between a sampling dose and the PK collection was 24.4 hours (5.8, 30.0) for breast milk and 22.4 hours (2.8, 29.9) for plasma.

3.2 Lactation PBPK Model Development

The base model overpredicted clearance (Supplement I, Figure S1, Panel A). Hepatic clearance was optimized from 1.22 to 0.89 1/minute. No other parameters were optimized. The final model showed good agreement with development and validation data (Supplement I, Figure S1, Panels B and C).

A sensitivity analysis revealed that of all physiochemical parameters evaluated, the breast milk AUC∞ was most sensitive to permeability, M/P ratio, unbound fraction, specific clearance, lipophilicity, and liver-associated parameters (Supplement I, Figure S2 and Table S3). No other parameters caused a ≥ 10% change in key PK parameters.

3.3 Evaluation of Lactation PBPK Models

We used the final model to simulate breast milk and plasma exposures following a single 4 mg dose of IV ondansetron in 1000 lactating women who were two days postpartum. Model predictions showed good agreement with observed data from the 55 women who contributed breast milk and plasma samples after a single 4 mg IV dose of ondansetron (Figure 3) and 23 women who contributed breast milk and plasma samples after multiple doses (Supplement I, Figure S3).

The GOF plots show approximately equal distribution around the line of unity except at higher concentrations, where the model tended to underpredict exposure (Figure 4, Panels A and B). Residuals were equally distributed around zero (Figure 4, Panels C and D). When averaged over all simulations, the breast milk MPE was 18.4% and MAPE was 53.0%. The plasma MPE was 32.5% and MAPE was 43.2%.

3.4 Model-predicted Ondansetron Exposure in Breast Milk

The median (range) predicted maximum concentration in breast milk was 20.2 ng/L (13.1, 83.6) and occurred at 0.5 hours after the dose. The estimated DID was 0.005 mg/kg/day. The RID compared to the standard maternal dose was 3.3% and compared to the standard infant dose was 1.6%. There were no adverse events noted in infants exposed to ondansetron in the CUDDLE study.

4. Discussion

In special populations such as lactating women, the use of PBPK modeling techniques is increasing as a method to address the challenges of conducting intensive PK studies in these populations and to better understand PK changes in the absence of sufficiently informative clinical data. However, there are currently less than a dozen examples of using PBPK lactational modeling to describe infant exposure from breast milk in the literature[41,42] and no established template for modeling drug passage from the blood to breast milk.

We established this model as a general PBPK model to quantitatively predict ondansetron transfer into breast milk. This model was built using a pregnancy model as a template and evaluated using in vivo concentration data from plasma and breast milk in lactating women. Predictions were based on a virtual lactating population we developed that included anatomic and physiological changes that occur after delivery. Changes in drug distribution during structural model development were primarily driven by changes in permeability, fraction of unbound, specific clearance, and M/P ratio. Ondansetron concentrations in breast milk were well predicted by this model, with observed values falling within a 35% error range of simulated data. Interindividual variability was not completely captured by the model as evidenced by the higher MAPE and is a limitation. Improved accounting of individual anatomic and physiologic changes is likely to improve predictions.

Infant ondansetron exposure was estimated using this model. The model-predicted DID was <5% of the maternal dose. Estimated DID and TID were calculated assuming the infant receives 200 mL of breast milk per day according to current FDA guidelines. These guidelines likely overpredict feeding volumes early postpartum and therefore are

conservative estimates of infant exposure. Although ondansetron is not FDA labeled for infants under 6 months of age, pediatric dosing guides recommend a starting dose of 0.1 mg/kg every 8 hours (0.3 mg/kg/day) in infants. This recommended dose is ~2 orders of magnitude higher than the predicted dose from breast milk (0.005 mg/kg/day). Even calculating RID using a single dose in the denominator results in a dose far less than the labeled dose. These comparisons suggest that breastfeeding should be safe.

There are limitations that should be noted with this model. First, *in vivo* PK data were acquired 1) within the first week after delivery, 2) after intravenous dose administration 3) at a limited number of timepoints, and 4) several hours after the dose. Additional data are necessary to evaluate models throughout the postpartum period and at earlier timepoints post-dose. Second, the calculated M/P ratio was slightly overpredicted compared to the observed ratio within the first week after delivery: 0.89 versus 0.95. This overprediction in M/P ratio may result in overprediction of infant exposure. This overprediction may be due to intraindividual differences in the relative lipid content of breast milk. Additional data are necessary to differentiate between foremilk and hindmilk. A third limitation is that the majority of extant literature describing CYP activity does not do so within the first 6 weeks postpartum. This model initially assumed that CYP activity during the first week postpartum was equivalent to activity during the end of pregnancy. Hepatic clearance was optimized in our final model and the result (0.89 1/min) was between the 3rd trimester pregnancy value (1.22 1/min) and the non-pregnant value (0.78 1/min).[17,20] GFR is also known to decrease after delivery and could have contributed to decreased clearance.[43] However, limited data suggest that GFR does not substantively change during the first week postpartum.[44,45] For this reason we assigned all of the decreased clearance to hepatic clearance. As additional data become available (e.g., if model is developed for a drug that is exclusively renally cleared), we expect improved accuracy in postpartum model parameters. A fourth limitation is that the current model does not include an explicit excretion mechanism from the milk sub-compartment and does not dynamically change the milk volume in the breast. The assumptions were 1) that change in molar drug clearance from a single feeding was much less than the total molar drug amount in the body and 2) drug concentrations reached equilibrium within the first hour after a feeding. Although this model adequately predicted ondansetron concentrations in breast milk, addition of a clearance mechanism for breast milk and accounting for refilling of breast milk volume may be of greater relevance for other drugs where passage into breast milk is slower. A fifth limitation is that infant weight was modeled after the 50th percentile of the World Health Organization growth charts. Data for these charts was collected exclusively from the United States, which introduced a systematic bias into calculations. Additionally, the use of the 50th percentile rather than a normal distribution around the median forced a central tendency and reduced the between subject variability. A sixth limitation is that the model is underpredicting at higher concentrations. This underprediction may be due to overprediction of the volume of distribution or underprediction of the fraction of unbound ondansetron. Our approach assumes a perfusion–rate-limited model where each tissue or organ represents a well-stirred compartment.[46] This implies that drug reaching the tissue or organ is instantaneously distributed in the whole volume of the physiological space. In many cases this will result in an overestimate of Cmax. The other possibility is that we overpredict

the volume of distribution (e.g., organ volumes, protein binding). Because of the limited observed data in the Cmax period, we were not able to optimize this estimate. One final limitation is that the structural model assumed that drug transfer to breast milk was only from the plasma. Drug transfer could also occur between the interstitial space and breast milk; however, the assumption was that this pathway was of minor relevance.

Additional steps are being taken to refine the described lactation PBPK model for future work. The next steps in model development will be to 1) add a mechanism for clearance of breast milk 2) simulate infant exposure beyond the first week postpartum, 3) develop a linked maternal/infant PBPK model to predict exposure in infants, and 4) compare infant predictions with observed infant data collected as part of the CUDDLE study. We are currently studying 30 drugs in the CUDDLE study and will model infant exposure and submit the data to the FDA for consideration of amended product labeling.

Both predicted and observed data demonstrate that ondansetron should be a safe for breastfed infants if used by lactating women. Because obtaining PK data is challenging during the early postpartum period and modeling of drug passage into human breast milk has been limited, [22] we report the development of a generic lactation PBPK model. We further report a virtual postpartum population database for simulations in PK-Sim; both the generic PBPK model and the postpartum population database are freely shared on GitHub for further applications to other drugs. Here we investigated ondansetron pharmacokinetics; these model predictions adequately described ondansetron passage into breast milk. Lactation PBPK models could help to improve the mechanistic understanding of drug pharmacokinetics in postpartum women including the drug amount ingested by the infant during breastfeeding. Ultimately, this could support informed decision-making when clinical data are sparse, missing or conflicting in this vulnerable population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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11. Data Availability Statement

The authors are unable to share the clinical data on ondansetron supporting the results of the results of this study. Models will be made available on GitHub (https://github.com/Open-Systems-Pharmacology).

8. References

1. Acevedo M, Pretini J, Micelli M, Sequeira G, Kerzberg E. Breastfeeding initiation, duration, and reasons for weaning in patients with systemic lupus erythematosus. Rheumatol Int. Jul 2017;37(7):1183–1186. doi:10.1007/s00296-017-3750-1 [PubMed: 28540416]
2. Ito S, Lieu M, Chan W, Koren G. Continuing drug therapy while breastfeeding. Part 1. Common misconceptions of patients. Can Fam Physician. Apr 1999;45:897–9. [PubMed: 10216783]
3. Matheson I, Kristensen K, Lunde PK. Drug utilization in breast-feeding women. A survey in Oslo. Eur J Clin Pharmacol. 1990;38(5):453–9. [PubMed: 1974205]
4. Saha MR, Ryan K, Amir LH. Postpartum women's use of medicines and breastfeeding practices: a systematic review. Int Breastfeed J. 2015;10:28. doi:10.1186/s13006-015-0053-6 [PubMed: 26516340]
5. Schirm E, Schwagermann MP, Tobi H, de Jong-van den Berg LT Drug use during breastfeeding. A survey from the Netherlands. Eur J Clin Nutr. Feb 2004;58(2):386–90. doi:10.1038/sj.ejcn.1601799 [PubMed: 14749761]
6. Stultz EE, Stokes JL, Shaffer ML, Paul IM, Berlin CM. Extent of medication use in breastfeeding women. Breastfeed Med. Sep 2007;2(3):145–51. doi:10.1089/bfm.2007.0010 [PubMed: 17903100]
7. Fortinguerra F, Clavenna A, Bonati M. Psychotropic drug use during breastfeeding: a review of the evidence. Pediatrics. Oct 2009;124(4):e547–56. doi:10.1542/peds.2009-0326 [PubMed: 19736267]
8. National Library of Medicine (US). Ondansetron. March 31, 2021. Accessed March 31, 2021. https://www.ncbi.nlm.nih.gov/books/NBK500798/
9. Gentile S. Clinical utilization of atypical antipsychotics in pregnancy and lactation. Ann Pharmacother. Jul-Aug 2004;38(7–8):1265–71. doi:10.1345/aph.1D485 [PubMed: 15150376]
10. Byrne JJ, Spong CY. "Is It Safe?" - The Many Unanswered Questions about Medications and Breast-Feeding. N Engl J Med. Apr 4 2019;380(14):1296–1297. doi:10.1056/NEJMp1817420 [PubMed: 30943334]
11. Chaves RG, Lamounier JA, Cesar CC. Factors associated with duration of breastfeeding. J Pediatr (Rio J). May-Jun 2007;83(3):241–6. doi:doi:10.2223/JPED.1610 [PubMed: 17486198]
12. Sachs HC, Committee On D. The transfer of drugs and therapeutics into human breast milk: an update on selected topics. Pediatrics. Sep 2013;132(3):e796–809. doi:10.1542/peds.2013-1985 [PubMed: 23979084]
13. Berlin CM, Briggs GG. Drugs and chemicals in human milk. Seminars in fetal & neonatal medicine. Apr 2005;10(2):149–59. doi:10.1016/j.siny.2004.09.016 [PubMed: 15701580]
14. Long L, Montouris G. Knowledge of women's issues and epilepsy (KOWIE-II): a survey of health care professionals. Epilepsy Behav. Feb 2005;6(1):90–3. doi:10.1016/j.yebeh.2004.11.006 [PubMed: 15652739]
15. Abduljalil K, Badhan RKS. Drug dosing during pregnancy-opportunities for physiologically based pharmacokinetic models. Journal of pharmacokinetics and pharmacodynamics. Aug 2020;47(4):319–340. doi:10.1007/s10928-020-09698-w [PubMed: 32592111]
16. GlaxoSmithKline. ZOFRAN (ondansetron hydrochloride): Highlights of prescribing information. Accessed February 2, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020103s035_020605s019_020781s019lbl.pdf
17. Dallmann A, Ince I, Coboeken K, Eissing T, Hempel G. A Physiologically Based Pharmacokinetic Model for Pregnant Women to Predict the Pharmacokinetics of Drugs Metabolized Via Several Enzymatic Pathways. Clin Pharmacokinet. Jun 2018;57(6):749–768. doi:10.1007/s40262-017-0594-5 [PubMed: 28924743]
18. Dallmann A, Himstedt A, Solodenko J, Ince I, Hempel G, Eissing T. Integration of physiological changes during the postpartum period into a PBPK framework and prediction of amoxicillin disposition before and shortly after delivery. Journal of pharmacokinetics and pharmacodynamics. Aug 2020;47(4):341–359. doi:10.1007/s10928-020-09706-z [PubMed: 32748112]
19. Simpson KH, Hicks FM. Clinical pharmacokinetics of ondansetron. A review. J Pharm Pharmacol. Aug 1996;48(8):774–81. doi:10.1111/j.2042-7158.1996.tb03973.x [PubMed: 8887724]

20. Elkomy MH, Sultan P, Carvalho B, et al. Ondansetron pharmacokinetics in pregnant women and neonates: towards a new treatment for neonatal abstinence syndrome. Clin Pharmacol Ther. Feb 2015;97(2):167–76. doi:10.1002/cpt.5 [PubMed: 25670522]
21. GlaxoSmithKline. ZOFRAN (ondansetron hydrochloride) Injection: Prescribing Information. Accessed February 2, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020007s040,020403s018lbl.pdf
22. Anderson PO, Sauberan JB. Modeling drug passage into human milk. Clin Pharmacol Ther. Jul 2016;100(1):42–52. doi:10.1002/cpt.377 [PubMed: 27060684]
23. Negin Mortazavi S, Hassiotou F, Geddes D, Hassanipour F. Mathematical modeling of mammary ducts in lactating human females. J Biomech Eng. Jul 2015;137(7)doi:10.1115/1.4028967
24. Tee GJ. Surface Area and Capacity of Ellipsoids in Dimensions. New Zealand Journal of Mathematics. 2005;34:165–198.
25. Logometria Cotes R. Philosphical Transaction of the Royal Society of London. 1714;2(338)
26. Jindal S, Gao D, Bell P, et al. Postpartum breast involution reveals regression of secretory lobules mediated by tissue-remodeling. Breast Cancer Res. Mar 28 2014;16(2):R31. doi:10.1186/bcr3633 [PubMed: 24678808]
27. Figueroa JD, Pfeiffer RM, Patel DA, et al. Terminal duct lobular unit involution of the normal breast: implications for breast cancer etiology. J Natl Cancer Inst. Oct 2014;106(10)doi:10.1093/jnci/dju286
28. Ramsay DT, Kent JC, Hartmann RA, Hartmann PE. Anatomy of the lactating human breast redefined with ultrasound imaging. J Anat. Jun 2005;206(6):525–34. doi:10.1111/j.1469-7580.2005.00417.x [PubMed: 15960763]
29. Yeung CHT, Fong S, Malik PRV, Edginton AN. Quantifying breast milk intake by term and preterm infants for input into paediatric physiologically based pharmacokinetic models. Matern Child Nutr. Apr 2020;16(2):e12938. doi:10.1111/mcn.12938
30. Gardner H, Lai CT, Ward L, Geddes D. Changes in R0/Rinfinity ratio and membrane capacitance are associated with milk removal from the breast. PLoS One. 2018;13(12):e0208650. doi:10.1371/journal.pone.0208650
31. World Health Organization. Weight-for-age. World Health Organization,,. 16 April 2021, Accessed 16 April 2021, https://www.who.int/tools/child-growth-standards/standards/weight-for-age
32. Larsen LA, Ito S, Koren G. Prediction of milk/plasma concentration ratio of drugs. Ann Pharmacother. Sep 2003;37(9):1299–306. doi:10.1345/aph.1C379 [PubMed: 12921514]
33. Atkinson HC, Begg EJ. Prediction of drug distribution into human milk from physicochemical characteristics. Clin Pharmacokinet. Feb 1990;18(2):151–67. doi:10.2165/00003088-199018020-00005 [PubMed: 2318008]
34. Erickson T, Gill G, Chan GM. The effects of acidification on human milk's cellular and nutritional content. Journal of perinatology : official journal of the California Perinatal Association. May 2013;33(5):371–3. doi:10.1038/jp.2012.117 [PubMed: 22975981]
35. Tracy TS, Venkataramanan R, Glover DD, Caritis SN, National Institute for Child H, Human Development Network of Maternal-Fetal-Medicine U. Temporal changes in drug metabolism (CYP1A2, CYP2D6 and CYP3A Activity) during pregnancy. Am J Obstet Gynecol. Feb 2005;192(2):633–9. doi:10.1016/j.ajog.2004.08.030 [PubMed: 15696014]
36. Guidance for industry bioanalytical method validation (U.S. Dept. of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research) (2018).
37. Clinical Lactation Studies: Considerations for Study Design Guidance for Industry (U.S. Dept. of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research) (2019).
38. Lexicomp. Pediatric & Neonatal Dosage Handbook, 27th edition. 2020-2021 ed. 2020:2611.
39. Varvel JR, Donoho DL, Shafer SL. Measuring the predictive performance of computer-controlled infusion pumps. J Pharmacokinet Biopharm. Feb 1992;20(1):63–94. doi:10.1007/BF01143186 [PubMed: 1588504]
40. Dallmann A, Solodenko J, Ince I, Eissing T. Applied Concepts in PBPK Modeling: How to Extend an Open Systems Pharmacology Model to the Special Population of Pregnant Women.

CPT Pharmacometrics Syst Pharmacol. Jul 2018;7(7):419–431. doi:10.1002/psp4.12300 [PubMed: 29569837]

41. Schreiber JS. Predicted infant exposure to tetrachloroethene in human breastmilk. Risk Anal. Oct 1993;13(5):515–24. doi:10.1111/j.1539-6924.1993.tb00010.x [PubMed: 8259441]
42. Nauwelaerts N, Deferm N, Smits A, et al. A comprehensive review on non-clinical methods to study transfer of medication into breast milk - A contribution from the ConcePTION project. Biomed Pharmacother. Jan 29 2021:111038. doi:10.1016/j.biopha.2020.111038
43. Cheung KL, Lafayette RA. Renal physiology of pregnancy. Adv Chronic Kidney Dis. May 2013;20(3):209–14. doi:10.1053/j.ackd.2013.01.012 [PubMed: 23928384]
44. Hladunewich MA, Lafayette RA, Derby GC, et al. The dynamics of glomerular filtration in the puerperium. Am J Physiol Renal Physiol. Mar 2004;286(3):F496–503. doi:10.1152/ajprenal.00194.2003 [PubMed: 14612381]
45. Krutzen E, Olofsson P, Back SE, Nilsson-Ehle P. Glomerular filtration rate in pregnancy: a study in normal subjects and in patients with hypertension, preeclampsia and diabetes. Scand J Clin Lab Invest. Sep 1992;52(5):387–92. doi:10.3109/00365519209088374 [PubMed: 1514017]
46. Nestorov IA, Aarons LJ, Arundel PA, Rowland M. Lumping of whole-body physiologically based pharmacokinetic models. J Pharmacokinet Biopharm. Feb 1998;26(1):21–46. doi:10.1023/a:1023272707390 [PubMed: 9773391]
47. Yang SH, Yang KH, Lee MG. Gender differences in ondansetron pharmacokinetics in rats. Biopharm Drug Dispos. Oct 2008;29(7):406–13. doi:10.1002/bdd.627 [PubMed: 18696412]
48. Poulin P, Theil FP. Prediction of pharmacokinetics prior to in vivo studies. 1. Mechanism-based prediction of volume of distribution. J Pharm Sci. Jan 2002;91(1):129–56. doi:10.1002/jps.10005 [PubMed: 11782904]

5.

Study Highlights

- **What is the current knowledge on the topic?** Obtaining PK data is challenging during the early postpartum period and modeling of drug passage into human breast milk has been limited.
- **What question did this study address?** The goals of this study were to develop a generic lactation PBPK model for small molecule drugs (molecular weight < 900 g/mol) and to apply this model to ondansetron to predict ondansetron exposure in breast milk.
- **What does this study add to our knowledge?** A PBPK approach was used to develop a generic lactation PBPK model that can be applied to small molecule drugs and used this model to predict ondansetron pharmacokinetics in maternal plasma and breast milk. A virtual postpartum population database was developed for simulations in PK-Sim.
- **How might this change clinical pharmacology or translational science?** Lactation PBPK models could help to improve the mechanistic understanding of drug pharmacokinetics in postpartum women including the drug amount ingested by the infant during breastfeeding.

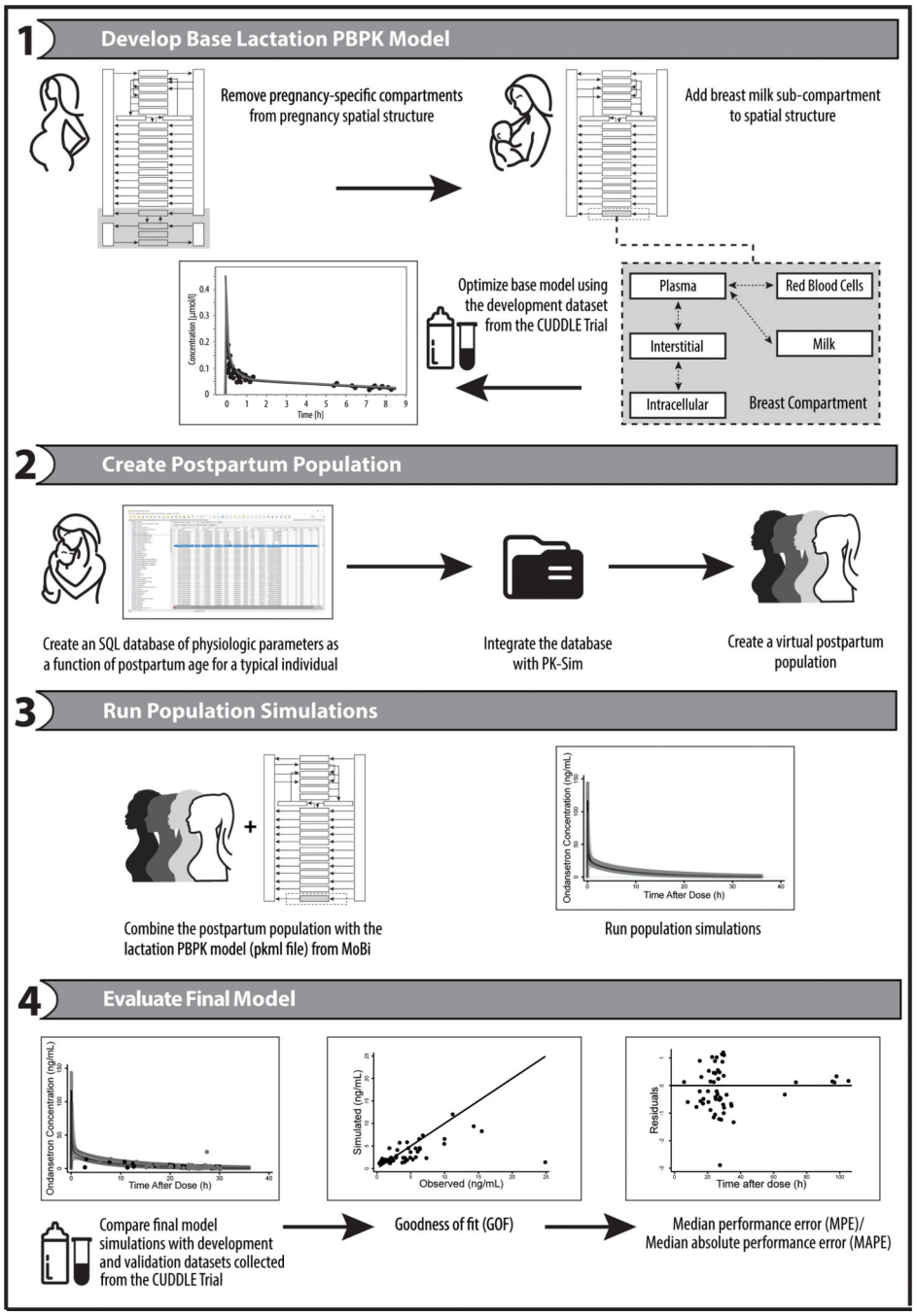

Figure 1:

Overview of the process for building the lactation PBPK model. The process includes four major components: 1) creation of the PBPK structure in MoBi, 2) creation of a postpartum population, 3) model simulation, and 4) model evaluation.

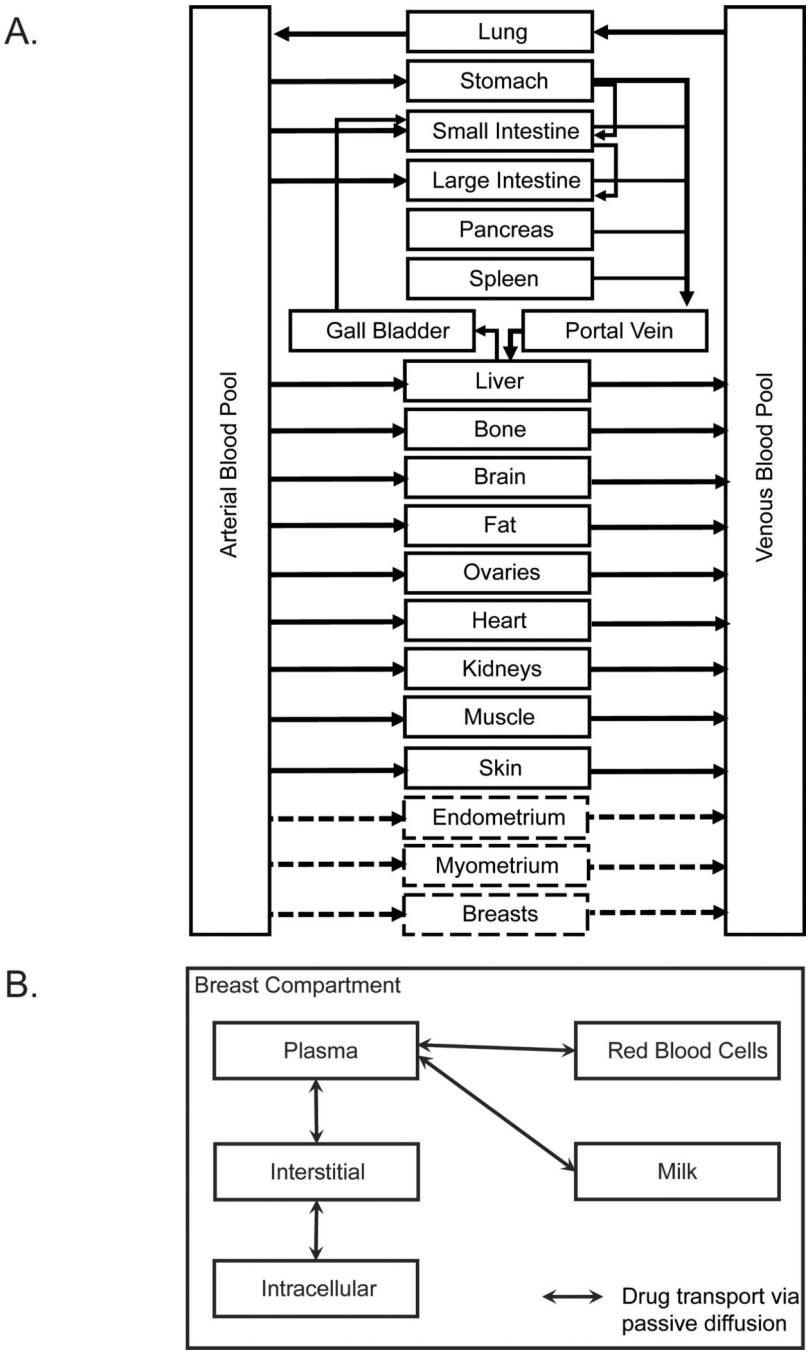

Figure 2:

Structure of the lactation physiologically based kinetic model. Panel A) shows the compartments and processes specific to the postpartum period are drawn with dashed lines and boxes. The lactation PBPK structure includes an additional three compartments compared to a non-pregnant woman, and four less compartments (e.g., maternal/fetal placenta, fetus, and amniotic fluid) compared to a pregnant woman model. Thick arrows represent drug transport via the blood flow and thin arrows drug transport via the gastrointestinal motility or via the biliary excretion pathway via the gallbladder. Panel B)

shows the structure of the breast compartment in the lactation model. A sub-compartment for milk was added to the breast compartment. Drug transfer is assumed to occur by passive diffusion between the plasma and milk sub-compartments.

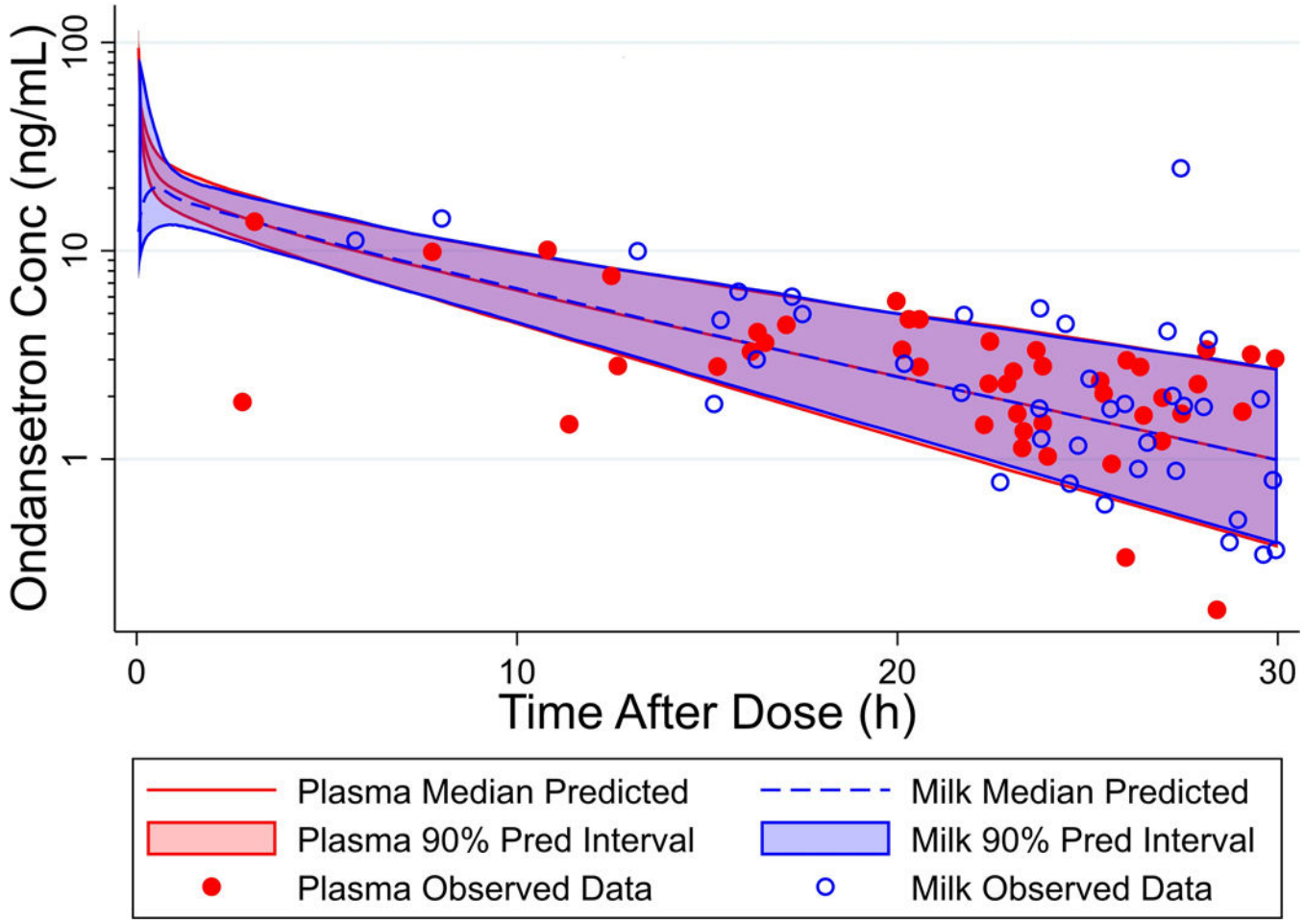

Figure 3:

Population PBPK model predictions of breast milk and plasma exposure following a single 4 mg IV dose of ondansetron in 1000 lactating women who were two days postpartum. Data from 55 lactating women from the CUDDLE study who received a single 4mg IV dose of ondansetron are overlayed.

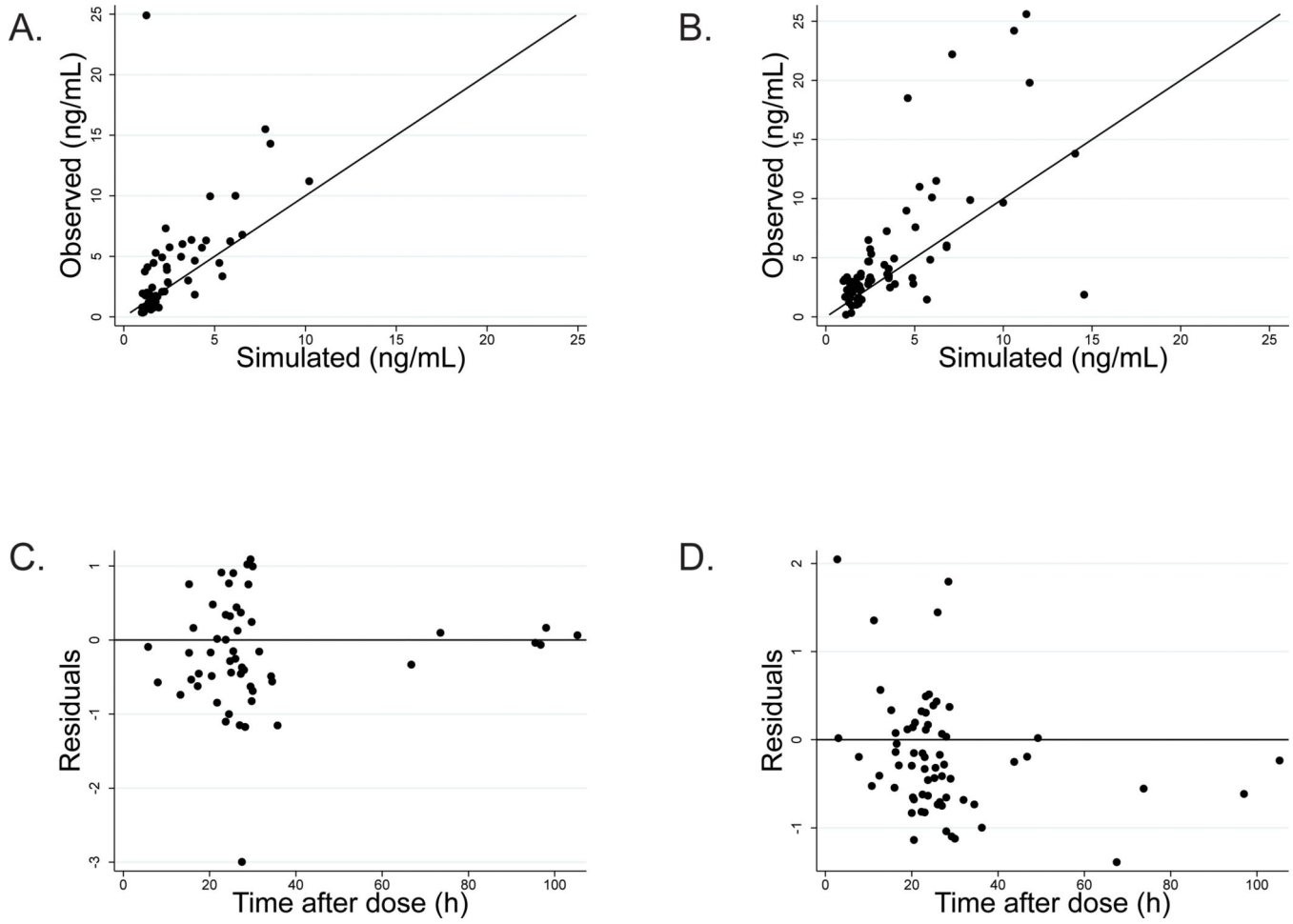

Figure 4:

The predicted milk (panel A) and plasma (panel B) concentrations are plotted against the observed plasma concentrations. The residuals versus time after first dose are shown for milk and plasma in panels C and D, respectively.

Table 1.

Summary of Input Parameters

Parameters [Unit]	Value	Reference
Molecular weight [g/mol]	293.4	PubChem
Lipophilicity [log units]	2.57	[17]
pK_a (acid)	7.80	[17]
pK_a (basic)	7.80	[17]
Fraction unbound	0.33	[17]
Major binding protein	Albumin	[19,47]
Protein binding scaling factor	0.96*	[18]
Solubility in water [μg/mL]	47.7	PubChem
Specific intrinsic clearance [min^{-1}]	1.22	[17]
GFR Fraction	0.40	[17]
Clearance fraction woman**		
CYP3A4	0.32 (160%)	[17]
CYP1A2	0.32 (63%)	[17]
CYP2D6	0.32 (200%)	[17]
Excreted in urine	0.04 (100%)	[17]
Organ-plasma partition coefficients	Breast	[48]
Model for estimating milk-to-plasma ratio	0.95*	Figure S2

*These values were assumed to be in the first week postpartum

**These values are not model input parameters, but the resulting model output for a typical woman

Table 2.

Demographics of Mothers who Contributed Samples

	Mothers (n = 78)
Age (years)	29 (19, 41)
PK sample collection (days after delivery)	1 (0, 5)
Weight (kg)	85.7 (59.6, 146.5)
BMI (kg/m²)	32.4 (24.0, 49.1)
Race (n (%))	
White	33 (42.3)
Black	38 (48.7)
Asian	2 (2.6)
Multiple	1 (1.3)
NR	4 (5.1)
Ethnicity (n (%))	
Hispanic	17 (21.8)
Not Hispanic	61 (78.2)

Values are median (range) for continuous variables and count (%) for categorical variables