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EXPERT REVIEW

Drugs in Lactation

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ABSTRACT One impediment to breastfeeding is the lack of information on the use of many drugs during lactation, especially newer ones. The principles of drug passage into breastmilk are well established, but have often not been optimally applied prospectively. Commonly used preclinical rodent models for determining drug excretion into milk are very unreliable because of marked differences in milk composition and transporters compared to those of humans. Measurement of drug concentrations in humans remains the gold standard, but computer modeling is promising. New FDA labeling requirements present an opportunity to apply modeling to preclinical drug development in place of conventional animal testing for drug excretion into breastmilk, which should improve the use of medications in nursing mothers.

KEY WORDS breastfeeding · drug excretion · human milk · modeling · pharmacokinetics

ABBREVIATIONS

AUC	Area under the concentration-time curve
CL	Total body drug clearance
Cp	Drug concentration in plasma
CYP2D6	Cytochrome P450 2D6
F	Bioavailability
FDA	U.S. Food and Drug Administration
HIV	Human immunodeficiency virus
I/M	Infant to maternal plasma concentration ratio
M/P	Milk to plasma concentration ratio
PBPK	Physiologically based pharmacokinetic
PLLR	Pregnancy and Lactation Labeling Rule
PopPK	Population pharmacokinetics
QSAR	Quantitative structure-activity relationship
RID	Relative infant dose
WHO	World Health Organization

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INTRODUCTION

Feeding infants with formula falls short of breastfeeding in many ways. For infants, formula use increases risks of otitis media, respiratory tract infections, gastroenteritis, necrotizing enteritis, sudden infant death syndrome, atopic dermatitis, inflammatory bowel disease, type 2 diabetes mellitus, leukemia, and obesity (1,2). These differences apply to infants in developing and developed countries.

The nursing mother also derives benefits from breastfeeding, such as more rapid uterine involution, decreased postpartum blood loss, fertility reduction, and decreased risks of breast and premenopausal ovarian cancer, type 1 and 2 diabetes mellitus, cardiovascular disease, and possibly osteoporosis and hip fracture later in life. Not breastfeeding or early cessation of breastfeeding also results in a higher risk of maternal postpartum depression. Annual excess deaths in the United States attributable to suboptimal breastfeeding are estimated to total 3340; of these, 78% are maternal. This excess morbidity leads to considerable costs for parents and the healthcare system. In the U.S., annual direct medical costs total $3 billion, 79% of which are maternal, and costs of premature death total $14.2 billion (1,2).

Research currently supports the recommendation that 6 months of exclusive breastfeeding followed by continued breastfeeding plus complementary foods for up to 2 years

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and beyond is best for infant health and development (1,3). Exclusive breastfeeding is defined as an infant's consumption of human milk with no supplementation except for vitamins and medications. The most recent data collected by the Centers for Disease Control and Prevention for 2014-2015 indicate that U.S. exclusive breastfeeding rates are only 44% at 3 months and 22% at 6 months (4). Many factors contribute to this shortfall, one of them being the use of medications by the nursing mother (5,6). In an extreme example, a study of mothers with systemic lupus erythematosus found that 45% of those who quit nursing early did so because of the medications they were taking (6). Many of these medications are said to be contraindicated because of a lack of data rather than because of known adverse effects. Overall, for the vast majority of medications used by nursing mothers, breastfeeding discontinuation is not necessary. However, information available on the safety of most medication use during breastfeeding is far from robust and completely absent for most new drugs. The need for more and better information on the excretion of drugs into breastmilk is clear.

Drug use during breastfeeding is different from use during pregnancy in some important ways. First, teratogenicity is not a concern during breastfeeding. Second, exposure of the nursing infant to a maternal medication is virtually always much less than exposure of the fetus to maternal medications. And third, large cohort studies, although useful, are not required to assess the safety of most drugs during breastfeeding. Relatively small pharmacokinetic studies can provide valuable information.

MATERNAL EFFECTS

Maternal effects of medications fall into 2 categories: maternal pharmacokinetic changes during lactation and drugs that affect lactation. Although a drug effect on maternal pharmacokinetics is a theoretical concern, one is hard pressed to find examples of clinically relevant changes to maternal pharmacokinetics caused by lactation. The most important examples are drugs that undergo major pharmacokinetic alterations during pregnancy that return to normal during lactation, such as with lamotrigine (7).

Several classes of drugs affect the milk supply. The most prominent drugs that suppress lactation are dopaminergic agents, such as drugs used for Parkinson's disease that decrease serum prolactin. Some of these drugs (e.g., bromocriptine, cabergoline) have been used specifically to inhibit lactation (8). Bromocriptine has been associated with severe maternal adverse cardiovascular effects, including death, and is no longer recommended for this use (9). The use of cabergoline for lactation suppression is considered "off-label". Sympathomimetic vasoconstrictors such as pseudoephedrine also decrease serum prolactin and milk output. A single 60 mg oral dose of pseudoephedrine decreased milk output by 24% over the following 24 h in one study (10). Anticholinergic drugs inhibit lactation in animals, apparently by decreasing growth hormone and oxytocin secretion (11,12). They also reduce serum prolactin in nonnursing women and lactation suppression has been reported with oxybutynin in postmarketing surveillance by the manufacturer (13). First-generation antihistamines in relatively high doses can decrease basal serum prolactin in early postpartum women (14). High-dose estrogens and androgens were used to suppress postpartum lactation in the past, but currently the dose of estrogen in oral contraceptives necessary to interfere with lactation and the postpartum timing of estrogen-containing contraceptive introduction are of greater concern (15).

Drugs and herbs that increase lactation are known as galactogogues. The most commonly used pharmaceutical galactogogues are domperidone and metoclopramide, which increase serum prolactin. Although prolactin is required for lactation, increasing prolactin above a minimal required level does not markedly enhance milk output. Original research and meta-analyses of galactogogue studies have generally found marginal benefits for domperidone and little to no good evidence of efficacy for other drugs or herbals (16,17). Domperidone does have some stong proponents, but it is not approved by the US Food and Drug Administration, primarily because of its small but important risk of death from drug-induced cardiac arrhythmias (18).

PASSAGE OF DRUGS INTO MILK

Breast Factors

The basic concepts of drug passage into breastmilk were elucidated through animal research in the 1950's and 60's (19,20). Mammary epithelial cells in the alveolus form a semi-permeable lipoid membrane separating plasma from breastmilk (Fig. 1). During the colostral phase (~3-4 days postpartum), the spaces between epithelial cells are relatively open, allowing large molecules (e.g., maternal immunoglobulins) to pass readily from the maternal circulation to the breastmilk. Following the colostral phase (~1 week postpartum), the pores are closed and only molecules with molecular weights of less than about 200 daltons pass readily through the pores into breastmilk. Larger molecules must pass across the membrane by passive diffusion down a concentration gradient formed by the nonionized, unbound drug on each side. Very large and highly charged drug molecules (e.g., amphotericin B, heparins) appear to be mostly unable to pass across this membrane. However, overt mastitis and possibly other maternal inflammatory conditions, can cause membrane disruption and allow lipids, large endogenous molecules and drugs to pass into milk in greater than expected amounts (21,22). Subclinical mastitis, found in 23% of women in one study,

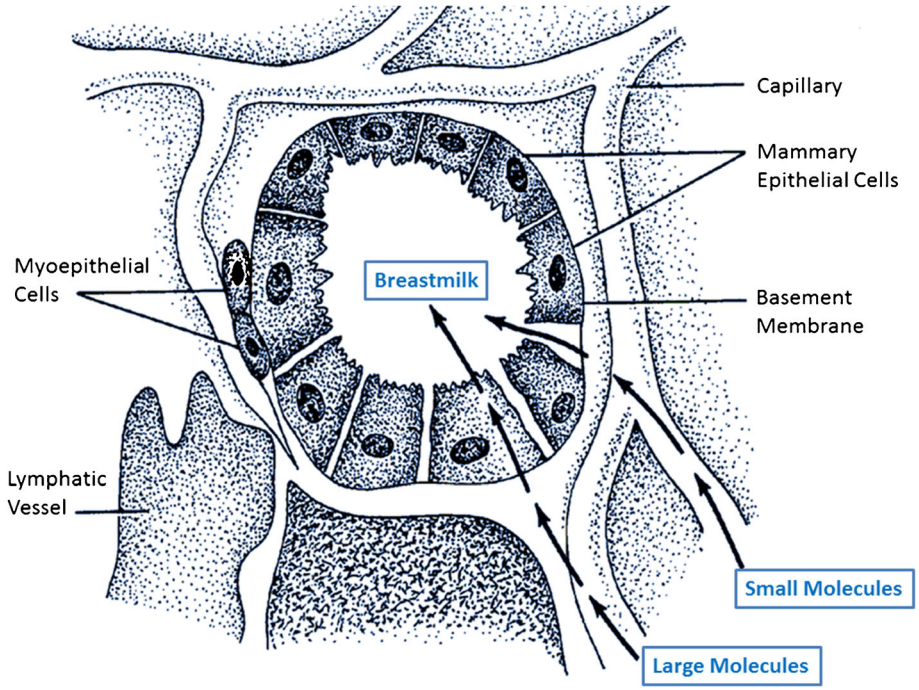

Fig. 1 The mammary alveolus. After the colostral phase, small molecules can pass through pores in the basement cell membrane and large molecules diffuse through the membrane.

allows the leakage of small amounts of large molecules into breastmilk (23).

Steady-State Physicochemical Factors

Both blood and breastmilk are complex fluids, so factors other than molecular size affect the net passage of drugs into milk. Because the *p*H of milk is typically slightly acid (*p*H 7.1-7.2) relative to that of plasma, *p*H partition theory predicts that the ionized form of weak bases will concentrate in breastmilk. Conversely, weak acids are somewhat inhibited from passing into milk. This ion trapping affects weak acids with a *p*Ka of 8 or less and weak bases with a *p*Ka of 6 or greater (24). Weaker acids and bases act as nonelectrolytes and do not undergo ion trapping. The partitioning of weak acids and bases is affected by milk *p*H, which can vary considerably. In one study of 100 milk samples, the *p*H of the milk varied over a wide range from day to day from values of 6.7 to 7.3 with a mean *p*H of 7.09. A small increase of *p*H in hindmilk (last milk of a feeding) compared to foremilk (first milk of a feeding) was also found (25).

Protein binding appears to be one of the strongest determinants of drug passage into breastmilk. Both plasma and breastmilk contain proteins that can bind drugs. The total plasma protein concentration is approximately 75 g/L, whereas human milk contains 8 to 9 g/L of protein. Of the plasma proteins, 45 g/L is albumin, a major drug-binding protein. The albumin concentration in milk is only about 0.4 g/L. The most abundant proteins in milk are casein, alpha-lactalbumin, lactoferrin, and immunoglobulin A. Casein is apparently the predominant drug-binding protein, but none of these milk proteins binds drugs well. Quantitatively important binding of drugs to milk proteins does not occur except in the case of drugs that are also extensively bound to plasma proteins. The net effect of protein binding is that highly protein-bound drugs tend to remain in the plasma and to pass into the milk in only low concentrations (26–28). One analysis of 38 widely used drugs found that plasma protein binding of 85% or greater generally indicated that infants would not have measurable plasma drug concentrations, with two possible exceptions, diazepam and fluoxetine (28). Both of these drugs have long half-lives and active metabolites.

Another important factor is that the fat composition of breastmilk changes over time. The average fat content in foremilk is 32 g/L and in hindmilk is 56 g/L (29). Fat content varies by time of day, with higher concentrations during the day and evening than during the night and morning (30). Also, manually expressed milk has about a 25% higher fat content than milk expressed with a breast pump (31). The fat content of breastmilk drifts slowly downward over the course of lactation to about 27 g/L at 6 months postpartum (29).

Milk fat can concentrate lipid-soluble drugs, causing the total amount of drug in milk to increase. For highly lipid-soluble drugs such as diazepam and phenytoin, well over half of the total amount of drug in breastmilk is found in milk fat (32,33). Because of the variability of the fat content of milk, highly fat-soluble drugs can have higher concentrations in milk at different times of the feeding and the day. These tendencies support the notion that a complete 24-h milk collection is optimal for studying drug excretion into breastmilk, especially for fat-soluble drugs. Nevertheless, because the

amount of fat in milk is small compared with the total volume of milk, the net clinical effect of lipid partitioning is relatively minor for most drugs.

A few drugs and chemicals undergo active secretion into breastmilk by transporters. Active transport is generally inferred when the milk to plasma (M/P) concentration ratio is markedly (usually at least 2-fold) greater than predicted by *p*H partition theory. The only transporters in humans known with some certainty to actively transport drugs into breastmilk are the sodium iodide symporter (iodide, perchlorate) and breast cancer resistance protein (acyclovir, cimetidine, methotrexate, nitrofurantoin and a few others), but these drugs appear to be exceptions to the rule that most drugs passively diffuse into breastmilk. (34–37).

In vitro studies on human mammary gland epithelial cells have identified transporters of organic cations (OCTs) in breast tissue of nonlactating women (38,39). However, it is not clear if these assays accurately represent the lactating mammary gland. A unique method of modeling active transport in which an electric gradient across the mammary epithelial cell provides the motive force to concentrate cimetidine in breastmilk has been proposed (40). This work is preliminary and requires further testing and validation.

Nonsteady-State Physicochemical Factors

The previous discussion relates primarily to steady-state conditions with constant maternal plasma levels. Because constant plasma concentrations are the exception during drug therapy, other factors must be taken into account during intermittent drug administration to the mother. The physicochemical factors that determine the rate of passage into milk appear to be the drug's lipid solubility and molecular weight. Lipid solubility is important because the drug must dissolve in the lipoid mammary epithelial cell membrane on both entering and exiting the cell, whereas low molecular weight favors rapid diffusion across the aqueous interior of the cell or passage through membrane pores (19,24). The rate of blood flow to the breasts might also affect the rate of passage into milk for some drugs, although this phenomenon has not been well studied.

Drugs that enter the milk rapidly achieve a peak concentration in milk sooner than drugs that enter slowly. For example, the alcohol (molecular weight 46 daltons) concentration in breastmilk closely parallels maternal plasma concentrations, probably because it equilibrates rapidly through the pores in the membrane separating blood and breastmilk (41). The larger (molecular weight 309 daltons) and nonpolar alprazolam has a peak breastmilk concentration that occurs at 1.1 h after the dose and about 0.5 h after the peak maternal plasma concentration (42). But the similar sized penicillin V (molecular weight 350 daltons), is a polar weak acid that equilibrates slowly and does not achieve peak breastmilk milk concentrations until more than 5.4 h after a dose in the absence of mastitis (21). Because milk is produced and periodically emptied from the breast during nursing, drugs that equilibrate slowly may never achieve high concentrations in breastmilk.

Another factor that comes into play during intermittent drug administration is the retrograde diffusion of drugs from breastmilk to maternal plasma. As the mother eliminates a drug and the unbound plasma concentration falls below that in breastmilk, the direction of diffusion reverses. Animal studies clearly indicate that drugs instilled into the udder pass out of the milk and are detectable in the plasma (43–45). The rate and extent of passage appear to be determined by the same physicochemical factors governing passage from the plasma into milk (46).

INFANT DRUG METABOLISM

Infants do not absorb, metabolize and eliminate drugs the same as adults (47,48). Neonates can absorb some large molecules, such as proteins (49,50). Although this ability allows absorption of IgG antibodies from breastmilk by the infant during the colostral phase (a primary advantage of nursing), absorption of some otherwise nonabsorbable drug molecules might also occur. This effect may be magnified in preterm infants, who have increased intestinal permeability (51). Other factors that can influence drug absorption are the infant's higher gastric *p*H, slowed gastric emptying time, reduced amounts of bile salts and pancreatic enzymes, immature drug transporters, partial formula feeding, a developing intestinal microbiome, and possibly antibiotic use (48,51–53).

The affinity of neonatal plasma proteins for drugs is less than that of older infants and children, leading to increased free drug concentrations. Newborns also have a greater percentage of body water and extracellular fluid volume than older children and adults. Hepatic metabolic capacity is low for the first week of life, but matures fairly rapidly, although the various cytochromes P450 mature at different rates. Renal function matures over 6 months to adult levels, with glomerular filtration maturing more rapidly than tubular secretion (48).

The above factors can lead to prolonged drug half-lives in neonates that may allow drugs excreted into breastmilk to accumulate in the infant to unexpectedly high concentrations with repeated maternal administration. Simulations of environmental contaminant passage found that half-life was the most important factor in determining the infant's systemic exposure to chemicals through breastmilk (54).

Infant responses to medications are sometimes different from those of older children and adults. These differences may result from immature enzyme systems, differences in the number or affinity of drug receptors, immaturity of the nervous system, and increased permeability of some membranes such as the blood-brain barrier. Pharmacogenetic

differences between individuals can also play a role in infant susceptibility to drug effects (55–57).

The continuously maturing infant metabolic and excretory pathways and pharmacodynamics mean that the age of the infant has a great effect on the infant's drug exposure. Analyses of adverse drug reaction reports in breastfed infants have found that about two-thirds of adverse reactions occur during the first month postpartum and more than three-quarters occur in the first two months (58,59).

LACTATION STUDIES

Animals

Animal models (e.g., mouse, rat), which are often used in preclinical studies and reported in official labeling, are not useful for predicting drug passage in humans because animal models often do not accurately reflect drug transfer in humans. Interspecies differences in milk protein and lipid composition, milk *p*H, drug transporter systems, and some anatomical differences mean that the amounts of drugs excreted into animal milk can differ markedly from human milk excretion (60,61). One study found that the median *total* M/P ratio (i.e., not unbound M/P) in mice is about twice as high as in humans (60) Some of this difference is caused by differences in chemical composition of milk such as milk lipid content (4-fold higher in mice than in humans), total milk protein content (10- to 20-fold higher in mice), and milk albumin content (10- to 20-fold higher in mice). Several of the drugs studied had total M/P ratios that were far higher in mice than in humans, for example atenolol (3-fold higher) and propylthiouracil (46-fold higher). The rat is another commonly used model. Rat milk likewise has about 4 times the fat content and 10 times the protein content of human milk (62,63).

Differences between animals and humans in *unbound* M/P ratios best reflect relative active transport between the species. In mice, some drugs have unbound M/P ratios much greater (metformin and terbutaline >8-fold greater) or much lower (triprolidine and verapamil <0.4-fold less) than in humans (60).

Humans

If only human data have direct clinical applicability, the issue of study design becomes important. Various study designs have been described to obtain breastmilk excretion data.

Milk-Only Design

The most commonly reported type of study is one in which only the amount of drug excreted into breastmilk is measured, referred to as the "milk only" design. This may be the only type of study necessary for drugs that have very low excretion into breastmilk and as few as 6 to 8 subjects may be adequate. After drug administration to a nursing mother, several timed milk samples are obtained after a single dose or over one dosage interval at steady-state to estimate the total drug excretion during the time period. The total can be measured either using complete milk sample collections or a more limited sampling scheme in which several timed aliquots are obtained. Collection of 5 or 6 milk samples at steady-state is probably adequate. The drug concentrations in the breastmilk samples are used to calculate an area under the milk concentration-time curve (AUC). Details on optimal sample collection and calculation of the AUC are reviewed in more detail elsewhere (64,65).

A complete 24-h milk collection from both breasts using an electric breast pump for each milk sampling is probably the most accurate method of calculating the AUC in milk (64,65). After aliquots are saved for analysis, the remaining breastmilk can be fed to the infant or discarded, depending on the perceived toxicity of the drug being studied. This method also allows calculation of the exact, rather than estimated, volume of milk that the infant ingests, providing a more accurate estimate of drug intake. If a 24-h milk collection is not possible, measuring concentrations of the drug in the foremilk and hindmilk portions of milk is a possible alternative.

The fat in milk can make analysis of drugs in milk problematic, from the standpoints of both of analytic methods and sample collection. Failure to account for the drug in milk fat can markedly distort the results of a study. The AUCs of water-soluble drugs might be underestimated if only hindmilk is collected, whereas the AUCs of fat-soluble drugs might be underestimated if only foremilk is sampled. If concentrations in both media are equal, sampling time is not a great concern. If drug concentrations are markedly different in the foremilk and hindmilk, mathematical adjustments based on the lipid content of the samples should be made. Regardless of the method used, it must be reported in order to allow proper interpretation of the results. The average milk concentration is calculated from the AUC in milk using the formula:

$$\text{Average concentration in milk} = \text{AUC}/\text{tau} \quad (1)$$

where tau is the time interval over which the AUC was measured.

Lactating Women Design

Measuring drug concentration in both maternal plasma and breastmilk can provide additional useful information. This is referred to as the "lactating women only" design. A common parameter calculated with this design is the ratio of the drug concentration in breastmilk to the concentration in the mother's plasma, called the milk/plasma or M/P ratio (Fig. 2). If several maternal plasma drug concentrations are measured during the collection of milk samples, one can calculate the AUC of the drug

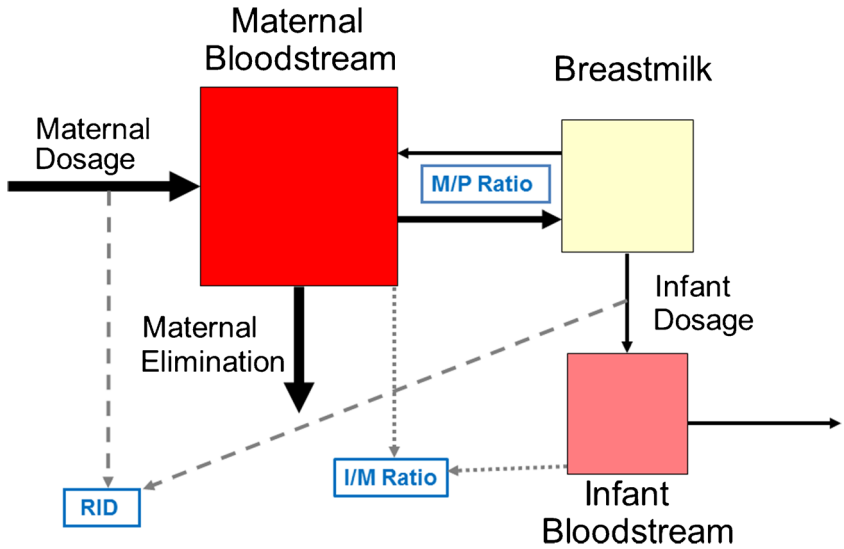

Fig. 2 Two-compartment model of drug passage into milk. Blue boxes indicate the various metrics describing the extent of drug passage. M/P = milk to plasma concentration ratio; RID = relative infant dosage; I/M = infant to maternal plasma concentration ratio.

in maternal plasma similarly to the AUC in breastmilk. The M/P ratio is then calculated by dividing the AUC of the drug in breastmilk by the AUC of the drug in the maternal plasma. The M/P ratio can be used to predict breastmilk concentrations based on actual or expected maternal plasma drug concentration with dosage regimens other than the one used to calculate the M/P ratio, and it can be used in the creation of more elaborate pharmacokinetic models that rely in part on Eq. 2.

$$\text{Drug concentration in milk} = \text{M/P x maternal plasma drug concentration} \quad (2)$$

If an average maternal plasma drug concentration is used, the average drug concentration in breastmilk will result. Sometimes the peak maternal plasma drug concentration is used to simulate a worst-case scenario. Two points about the M/P ratio are worth noting. First, simultaneous measurements of one milk and one maternal plasma drug concentration usually does not provide an accurate value for the M/P ratio because drug levels in maternal plasma and breastmilk usually do not rise and fall in parallel as shown in Fig. 3 (66). Second, from a clinical perspective, the M/P ratio does *not* predict the safety of a drug during breastfeeding (28,64). Although some authors have stated that drugs with an M/P ratio less than one are safe to use and those with an M/P ratio over 1 are not, there is absolutely no basis for this assertion. The M/P ratio should be seen only as a starting point for further calculations and modeling. Once the predicted drug concentration in milk is calculated, the average daily dosage of a drug that the infant will receive can be calculated using Eq. 3:

$$\text{Infant daily dosage} = \text{F} \times \text{milk drug concentration} \times \text{daily milk volume ingested} \quad (3)$$

where F is the bioavailability of the drug in infants.

The daily milk intake is routinely assumed to be 150 mL/kg for an exclusively breastfed infant. This value was enshrined by the World Health Organization (WHO) Working Group on Drugs and Human Lactation in 1988 (67). But, in fact, milk intake does not have a constant value–it varies with the age of the infant. Based on longitudinal data, breastmilk intake by exclusively breastfed infants in the United States on postpartum day 1 averages about 10 to 15 mL/kg. By day 4, the average value is 141 mL/kg/day, increasing to 163 mL/kg/day on day 7. The maximum average value of 176 mL/kg/day occurs at 28 days of age. By 56 days of age, the average decreases to 130 mL/kg/day. At 90 days of age, the value is 117 mL/kg/day and at 6 months of age, the average value for exclusively breastfeeding mothers is 108 mL/kg/day. The coefficient of variation in milk volume measurements is greater than 20% (68). Nevertheless, the value of 150 mL/kg/day is well established in the pharmacokinetic literature and it does provide a standard by which similar drugs can be compared to each other. Therefore, this standard value should be used to calculate values reported in the

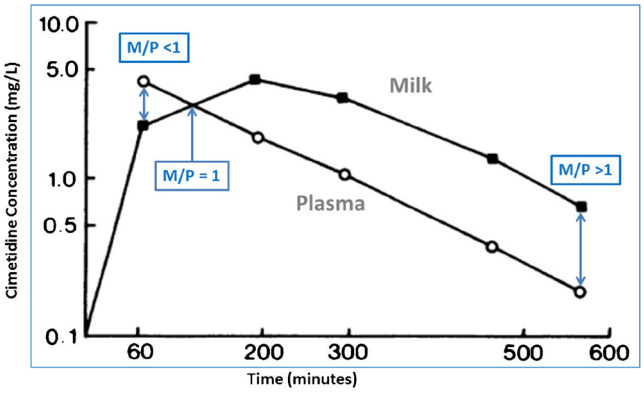

Fig. 3 Maternal plasma and breastmilk cimetidine concentrations after 400 mg orally, illustrating the necessity of using AUCs to calculate the M/P ratio. Modified from reference (66).

literature. If actual measurements of milk volume are made, these can be useful for evaluating exposure of the particular infant being studied and for informing a correlation between infant dosage and reported infant side effects (69).

Once the infant's drug dosage is calculated using one of the above methods, it would ideally be compared to the usual neonatal or infant dosage of the drug. Unfortunately, infant dosages are not established for a large portion of marketed drugs and almost never for new drugs. Therefore, the experts comprising the WHO Working Group and others proposed calculation of a value initially referred to the weight-adjusted percentage of the maternal dosage, now more commonly called the relative infant dosage or RID as illustrated in Fig. 2 (67,70). Equation 4 illustrates the correct method of calculating the RID. Occasionally, authors incorrectly calculate the RID using absolute (i.e., mg/day) rather than weight-adjusted dosages.

$$\mathrm{RID} = \frac{\text{Infant dosage(mg/kg/day)}}{\text{Maternal dosage(mg/kg/day)}} \times 100 \qquad (4)$$

The WHO Working Group further proposed that drugs with an RID greater than 10% of the lowest end of the weight-adjusted (i.e., mg/kg) maternal dosage might not be safe for the breastfed infant and those with an RID greater than 25% of this value should be avoided in nursing mothers. No empiric evidence was used to define these breakpoints, rather they represent a consensus of the Working Group.

Although the RID is currently accepted as a measure of safety of medication use during breastfeeding, it has numerous important shortcomings. One problem with the RID is that the dosage of the drug given to the mother can vary over a range. As the maternal dosage increases, so does the infant's dosage from the drug in breastmilk, but the RID usually does not change. So, the RID is poor at representing drug safety during breastfeeding for drugs with a wide dosage range, especially those with an RID near the 10% cutoff. In contrast, the RID of some drugs changes over time, even with a constant dose (71). This phenomenon has not been well studied, but pharmacokinetic simulation indicates that it might reflect the filling of a deep (and as yet unidentified) compartment (72).

As can be seen from Eqs. 3 and 4, the calculation of the RID assumes that the infant is exclusive breastfed. If this is not the case in a specific mother-infant dyad, the effective RID should be reduced proportionately. Other potential pitfalls of the RID include the possibility of differences in bioavailability of the drug between infants and adults. Importantly, the RID, lacks any consideration of the age of the infant, or inherent toxicity of the medication.

Mother-Infant Pair Design

For ideal pharmacokinetic modeling purposes, drug concentrations would be measured in the plasma of breastfeeding infants as well as maternal milk and plasma after maternal ingestion of a drug. This design, referred to as the "mother-infant pair" design, would compensate to a large degree for the differences in maternal and infant pharmacokinetics. For new drugs with no experience in nursing mothers and infants, ethical considerations usually require discontinuation of breastfeeding after maternal drug administration. This may not be acceptable for many mothers and can present some risk to the infant who receives formula. So, it is understandable that multiple infant blood samples are rarely obtained, and usually only when previous studies indicate that they would be necessary to determine infant safety. Infant plasma drug concentration measurements can be useful occasionally in individual infants suspected of having an adverse reaction from a drug in breastmilk. Another option is the use of so-called opportunistic blood samples (73). These are blood samples taken from the infant for routine care (e.g., serum electrolytes) that are saved for later analysis of drug concentrations. The utility of these samples may be enhanced if routine tests can be scheduled at optimal sampling times for the drug study.

Mothers who require the drug for their own clinical care may be more suitable subjects for the mother-infant pair design than mothers with no need for the drug. Methods of identifying nursing mothers who are taking medications are pregnancy exposure registries, breastmilk repositories, and infants in neonatal intensive care units who are being supplied breastmilk by their mothers. This latter method has the advantage of close monitoring of infants for any adverse effects of the drug in breastmilk (61).

When infant plasma drug levels are obtained, they can be used to calculate the ratio of the infant plasma drug concentration to the maternal plasma drug concentration or I/M ratio (Fig. 2). As with the RID, a drug that produces a steady-state I/M ratio less than 10% of the lower end of the therapeutic concentration range was considered acceptable and a ratio greater than 25% was considered to be unacceptable by the WHO Working Group, again with no empiric evidence (67).

The I/M ratio is most accurate when applied at steady-state for drugs having relatively long half-lives such that maternal and infant levels are not fluctuating substantially. When samples are obtained under these conditions, a reliable measurement from single trough blood samples from the mother and infant would probably suffice, although this has not been rigorously tested. For drugs that have a short half-life, multiple plasma samples are required to obtain average plasma concentrations or AUC measurements to derive a reliable I/M ratio.

Caution must be used in the timing of infant plasma samples if the mother was taking the drug during pregnancy. In general, much more drug is passed to the infant transplacentally than via breastmilk, so if the infant has high plasma drug concentrations at birth and the drug has a long half-life, the infant's plasma concentration in the early neonatal period can be a reflection of transplacental passage of the drug rather than intake from breastmilk.

As with the RID, the clinical applicability of the I/M ratio is partly determined by the inherent toxicity of the drug in question, which cannot be easily quantified. Some drugs with relatively high infant plasma drug concentrations have been found, preliminarily at least, to not be harmful to infant development. For example, breastfed infants whose mothers are taking the antiepileptic drug lamotrigine have plasma levels averaging 30% to 35% of maternal plasma levels. Nevertheless, one long-term follow-up study found that infants exposed to lamotrigine in breastmilk had slightly higher IQs and enhanced verbal abilities at 6 years of age than nonbreastfed infants (74). Ultimately, balancing the benefits and risks of maternal medications is more complex than pure mathematical modeling.

If a normal therapeutic or toxic plasma concentration is known, measurement of drug concentration in the plasma of breastfed infants is the most direct method of assessing infant risk. Short of measuring infant plasma concentrations, the average infant plasma concentration (Cp) can be estimated by dividing Eq. 4 by infant drug clearance:

$$\mathrm{Cp} = \mathrm{F} \text{ x infant daily drug dosage/CL} \tag{5}$$

Equations 1, 2 and 5 can be combined to create Eq. 6, which provides an estimate of the average infant plasma concentration.

$$\mathrm{Cp} = \mathrm{F} \times \mathrm{M/P} \times \text{maternal plasma drug concentration} \times \text{daily milk volume/CL} \tag{6}$$

The method above has been used occasionally in the literature to estimate infant plasma concentrations. However, the lack of developmental drug clearance values and clinically meaningful concentration cutoffs in infants for many drugs make this method difficult to apply.

MODELING OF DRUG PASSAGE

M/P Ratio Modeling

The prospect of predicting the concentration of drugs in infant plasma using only the physicochemical properties of the drug and known pharmacokinetic parameters is appealing. Modeling generally proceeds in two phases: prediction the M/P ratio followed by pharmacokinetic modeling of breastmilk drug concentrations and possibly infant drug exposure.

The most successful early attempt at predicting the M/P ratio from physicochemical properties was the phase distribution model. This model attempted to predict M/P ratios from drugs' *p*Ka, octanol/water partition coefficient, and plasma protein binding. The log-transformed phase distribution model was the state of the art for over 2 decades. But, several factors can potentially affect its predictive ability. The sensitivity of the phase distribution model to the method of measuring the octanol/water partition coefficient is a potential problem (75). Although good first approximations, the octanol/water partition coefficient and *p*Ka might not adequately characterize drug passage into breastmilk (76). Furthermore, drugs that are actively transported into milk are not accounted for in the phase-distribution model.

An alternative to the phase-distribution model is the quantitative structure-activity relationship (QSAR) methodology to predict the M/P ratio. This method empirically correlates molecular attributes such as polarity, number and negativity of ionizable groups, total polar surface area, hydrogen bonding, and presence of aromatic groups, to previously obtained M/P ratios from the published literature (77,78). These methods have been reviewed recently (79). In brief, a number of groups worldwide have proposed QSAR models and many of them appear to be improvements over the log-transformed phase distribution model, but they have not been compared to each other using well-validated human M/P ratio data. Some of the models appear to use proprietary data that make such comparisons more difficult. The relatively small number of properly performed human studies that accurately measure M/P ratios is an ongoing limitation to model testing.

Pharmacokinetic Modeling

The second phase of modeling involves pharmacokinetic models to describe the passage of drugs into breastmilk and ultimately plasma drug concentrations in the breastfed infant. Potential benefits of pharmacokinetic modeling techniques include predicting infant plasma drug concentrations obtained through breastfeeding without having to obtain large numbers of infant blood samples, and leveraging pre-existing knowledge of the drug's absorption, metabolism and excretion by infants. It can also lead to discovery of covariate factors that can influence passage of drugs into the breastmilk and infant drug exposure. In general, two types of modeling approaches have been used to analyze breastmilk data: top down, often using population-based pharmacokinetic (PopPK) modeling, and bottom up or physiologically based pharmacokinetic (PBPK) modeling.

Once pharmacokinetic parameters and their variability are estimated for these models, Monte Carlo simulation can be used to simulate large numbers of patients, integrating variability in breastmilk disposition as well as maternal and infant pharmacokinetic variability to define the lower and upper limits of the RID. Various dosage scenarios that could either minimize or maximize infant drug exposure can also be simulated.

Top Down Modeling

Top-down (PopPK) modeling is an empiric method of data analysis that can use data from a relatively modest number of samples (e.g., blood, breastmilk) from patients in a population to develop a pharmacokinetic model. It uses "standard" pharmacokinetic models (e.g., one-compartment, two-compartment models) with minor modifications to characterize breastmilk pharmacokinetics and typically has the goal of developing a simple, mechanistically plausible model that best describes observed maternal, breastmilk and infant drug concentration data. These analyses can also incorporate some pre-existing pharmacokinetic parameters from the literature. The ability of PopPK modeling to analyze a smaller number of samples per patient obtained under less rigidly controlled conditions than with traditional high-intensity sampling makes it a useful approach for the analysis of breastmilk drug concentrations. Samples obtained in different studies can be combined into a single analysis to enhance the power of the analysis.

PopPK modeling of breastmilk data has been reported for several drugs, including tramadol, fluoxetine, parecoxib, nifurtimox, nevirapine, piperaquine and azithromycin (80–88). Tramadol, fluoxetine and parecoxib all have active metabolites that were accounted for in the models.

In a paper using previously published data, the authors' model accounted for both fluoxetine and norfluoxetine (83). Simulation indicated that the median combined RID of the drug and metabolite was 5.9%, and the 99th percentile value was 23%. The simulation was useful for indicating that some infants will have a rather extensive exposure to fluoxetine and its active metabolite, which is consistent with several case reports of adverse effects from fluoxetine in breastfed infants (89). For nifurtimox, pharmacokinetic data from adults were used to create a model in the mother, then simulations were run using assumed M/P ratios of 1 and 6 to predict the range of possible exposures. These assumptions resulted in a prediction of a median RID of 0.19% with an M/P ratio of 1 and a 99th percentile RID of an acceptable 3.1% with an M/P ratio of 6 (86).

The nevirapine model was used to simulate infant plasma concentrations achieved with breastfeeding following administration to the mother at various times before delivery. The model indicated that higher infant doses would be needed for HIV prophylaxis if they were born less than 1 h after maternal nevirapine administration (90).

The azithromycin model is noteworthy because it provided estimates of both the maximum daily dosage and the cumulative dosage that the breastfed infant would receive after a single oral dose of a drug with a long half-life (88).

Bottom Up Modeling

Bottom-up modeling, such as with PBPK, is a method that uses a mechanistic approach to modeling to predict the behavior of drugs in the body. It requires no patient data input, but rather relies on known or estimated physiologic parameters. It integrates organ sizes, regional blood flows, enzyme activities and drug partitioning characteristics to predict regional drug concentrations over time. While the PBPK approach is not used to directly estimate pharmacokinetic parameters or fit the data to the model, the predicted concentrations from the PBPK model can be compared to observed concentrations.

PBPK modeling has been used to support new drug applications in the U.S. and Europe (91,92). With respect to breastfeeding, PBPK models have been most often used to simulate exposure to environmental chemicals (93,94). However, a few examples of drug simulations have been published. A PBPK model was described for codeine, a morphine pro-drug, use by nursing mothers (95,96). This drug was of interest because of the death of a breastfed infant whose mother was an ultra-rapid CYP2D6 metabolizer and taking codeine (97). The authors simulated morphine plasma concentrations in breastfed infants under various conditions of CYP2D6 metabolism and morphine metabolic rates. Both maternal extensive and ultra-rapid CYP2D6 metabolizer statuses were found to provide sufficient morphine and codeine to a breastfed infant to cause toxicity over a few days of continuous maternal use. Other PBPK models for lactational drug transfer have involved clonidine and lamotrigine, two drugs that have caused adverse reactions in breastfed infants (98,99).

The combined use of top-down and bottom-up modeling approaches in drug development for very young children has been advocated to leverage the strengths of each method (100). A recent study on escitalopram took this approach, using PopPK to analyze breastmilk escitalopram concentrations from 18 women. PBPK was then used to simulate the range of infant exposures to the drug in 1000 infants (101).

Potential Shortcomings of Modeling

Several infant factors make modeling of infant exposure levels and risk difficult. As discussed above, the breastfed infant is continually changing in milk intake and maturation of drug absorption, transport and elimination pathways. Pharmacogenetic differences also complicate modeling. For these reasons, when modeling is used, the results should be compared to at least breastmilk drug concentration measurements. If the model is extended to predict infant plasma concentrations, measured infant concentrations would be beneficial for model validation.

Regardless of how well pharmacokinetic studies or models perform in predicting infant dosage of drugs in breastmilk, they cannot paint a complete clinical picture. Drugs vary in their toxic potentials, making purely mathematical results less than definitive. Effects from the use of multiple maternal

medications simultaneously can result in additive side effects or drug interactions that alter the impact of the drugs. Finally, not all adverse drug reactions are related to dosage. Allergic drug reactions can occur with small amounts in breastmilk. Analysis of adverse reactions in breastfed infants indicates that about 20% of reported infant adverse reactions are probably not related to the dosage of the drug in breastmilk (59,89).

REGULATORY ISSUES

The U.S. Food and Drug Administration (FDA) has recognized the shortcomings of their old regulations promulgated in 1979, which allowed essentially only 2 standard labeling options. The options can be briefly summarized as, "do not breastfeed with this drug" and "use this drug with caution while breastfeeding", neither of which was very helpful to the prescriber. New labeling standards called the Pregnancy and Lactation Labeling Rule (PLLR) went into effect on June 30, 2015 and is scheduled to be fully implemented in 2020 (102). These standards recognize both the benefits of breastfeeding and the possible risks.

The new labeling regulations require a "Lactation" section in the package insert consisting of 3 parts: Risk Summary, Clinical Considerations, and Data. Under the Risk Summary subheading, regulations state, "If the data demonstrate that the drug does not affect the quantity and/or quality of human milk and there is reasonable certainty either that the drug is not detectable in human milk or that the amount of drug consumed through breastmilk will not adversely affect the breast-fed child, the labeling must state: The use of (drug name) is compatible with breastfeeding" (102). When there are insufficient data, the Risk Summary must state so. A statement regarding balancing drug risks with the benefits of breastfeeding is usually included.

After this statement, the Data section must summarize the drug's effect on milk production, what is known about the presence of the drug in human milk, and the effects on the breastfed child as well as the source(s) of the data (e.g., human, animal, *in vitro*). If human data are available, animal data are not included unless the animal model is specifically known to be predictive for humans. The PLLR does not specifically mention (nor prohibit) the use of pharmacokinetic models to inform lactation labeling. Finally, the Clinical Considerations section provides information on ways to minimize the exposure of the breastfed infant to the drug and potential drug effects in the breastfed infant, including recommendations for monitoring or responding to these effects.

PLLR is not all-inclusive, however. Over-the-counter drugs and drugs that were approved before June 30, 2001 are exempted from the labeling. There is no requirement that manufacturers perform studies on their drug during breastfeeding and it is unclear whether labeling will be updated in a timely fashion after 2020 as new data become available.

An important and unresolved issue from a regulatory perspective is the level of evidence needed before inclusion in the official labeling. Potential sources include conventional pharmacokinetic studies, observational studies, mining of patient care databases, case reports, and computational models. Much current clinical information on drug use during breastfeeding has been published in the form of case reports rather than well-controlled studies. Case reports can contain breastmilk or infant plasma concentration data, infant safety assessments or both. Whether to include case report data and which type to include in the official drug labeling seems to be an ongoing discussion at the FDA.

To address the lack of lactation data, the FDA issued a guidance document in 2005 for the drug industry on how to perform lactation studies (65). A follow-up meeting entitled, "Evaluation of the Safety of Drugs and Biological Products Used During Lactation" was held in April 2016, followed by a meeting summary published in 2017 (61).

SUMMARY

All health professions have a responsibility to help maximize breastfeeding in new mothers. One impediment is the lack of useful clinical data for many drugs, especially newer ones. The principles of drug passage into breastmilk are well established, but have not been optimally applied prospectively. Measurement of drug concentrations remains the gold standard, but computer modeling is promising. High precision is often not necessary, so computer modeling should be at least as useful as current flawed animal testing methods for premarketing assessment of the safety of drugs in nursing mothers. If a 10% exposure cutoff is used to predict safety, it does not matter greatly whether exposure is 0.1% or 3%. Achieving a prediction accuracy within one order of magnitude is probably adequate for most drugs, and current modeling techniques should easily exceed this level of accuracy. The FDA's new PLLR labeling requirements for lactation present an excellent opportunity to make use of modeling to meet the new requirements.

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