CHAPTER 5

Lactation Pharmacology

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OBJECTIVES

- Describe the principles of drug entry into human milk.
- Identify the factors of drug transfer from maternal circulation to breastmilk.
- Describe the calculations that help predict drug exposure to infants.
- Predict the risk of medication to the infant.
- Identify the toxicity of a drug to the infant.
- Describe the clinical implications of drug excretion during lactation.
- Describe the steps to minimize medication exposure to infants.
- Describe the monitoring of an infant with potential drug exposures.
- Describe galactogogues that stimulate milk production.
- Describe recreational and illegal substance use as it relates to breastfeeding.
- Describe topical use of medications on the breast.

DEFINITIONS OF COMMONLY USED TERMS

acid-base dissociation constant (pKa) Factor that determines the likelihood of a drug being trapped in the milk compartment, called ion trapping.
bioavailability A measure of how much medication reaches the plasma.
dalton Unit used in expressing the molecular weight of proteins, equivalent to atomic mass unit.
diffusion Transfer of molecules of a substance between the plasma compartment and the milk compartment.
lipid solubility Capability of a substance to dissolve in lipids, fats, or oils.
milk-to-plasma ratio Tool to evaluate the relative concentration of medication in the plasma compared to the milk compartment.
protein binding Degree to which a drug binds to the proteins within blood plasma. The less bound a drug is, the more efficiently it can traverse cell membranes or diffuse.

Overview

Although our understanding of drug transfer into human milk has advanced over the past 20 years, it is still rather obscure. While we understand some of the basic requirements for medication transfer into milk, we are still unable to adequately predict with certainty how much of a drug is likely to transfer into this compartment. Of the several published kinetic modeling systems, most are highly sophisticated and predict milk levels rather poorly. Thus, we are still dependent on rare clinical trials to accurately determine the level of a drug in milk. Unfortunately, far fewer than 30 percent of drugs currently marketed have been studied in relation to breastfeeding. While the U.S. Food and Drug Administration (FDA) is increasing pressure on pharmaceutical firms to do breastfeeding studies on new drugs, many older drugs have still not been studied in breastfeeding mothers.

The most difficult task is to understand and predict the overall safety of a medication that might transfer into milk. In essence, the question is how the infant will respond to the dose of medication found in the milk. Thus, the level of evidence needed to declare a medication safe is often not attainable. Most drugs are generally considered compatible with breastfeeding, although we are unable to predict the safety, with certainty, of some drugs. This chapter reviews the science behind lactation pharmacology, describes the process of risk assessment as it applies to infant drug exposure, and provides the reader with the proper tools to evaluate a drug.

The use of medications in breastfeeding mothers is often complicated in encounters with attending physicians. The prescribing provider has different priorities and makes the argument that a new medication is necessary to the health of the parent. If the physician does not properly address the issue of breastfeeding safety, the mother may be forced to seek outside counsel and ultimately have to decide whether the benefits of the drug outweigh the importance of breastfeeding. In other words, if it is assumed that the drug is both hazardous and necessary, the question becomes whether the breastfeeding benefit to the baby exceeds the drug exposure risk to the baby. There is not always an adequate answer for this conundrum.

Any use of the term *mother, maternal,* or *breastfeeding* is not meant to exclude transgender or nonbinary parents who may be breastfeeding their infant.

I. Kinetics of Drug Entry into Human Milk

A. The amount of drug excreted into milk depends on a number of factors. Drugs enter the milk primarily by diffusion, driven by equilibrium forces between the maternal plasma compartment and the maternal milk compartment.[1]
   1. Medications enter the milk by transferring from the maternal plasma, through the capillary walls, past the alveolar epithelium, and into the milk compartment.[2]
   2. During the first 4 days postpartum, large gaps exist among alveolar cells (see **FIGURE 5-1**).
   3. These gaps might permit enhanced drug entry into milk during the colostral period, while the absolute amount of the drug in the milk might still be quite low.
   4. After 4 to 6 days, the alveolar cells enlarge, shutting off many of the intercellular gaps, and the amount of drug entry into the milk is reduced.
   5. Because the alveolar epithelium has rather tight junctions, most drugs must dissolve through the bilayer membranes of the alveolar cells before they can enter the milk.
   6. It is difficult for most medications to dissolve through the bilayer lipid membranes, particularly for drugs that are ionic or polar.
   7. The more lipid soluble a drug is, the greater its capability to penetrate into the milk.
   8. Drugs that are active in the central nervous system generally attain higher levels in the milk compartment because their chemistry is ideal for entry. Ideal physicochemistry includes higher lipid solubility, smaller molecular weight, and higher plasma levels.
   9. Drugs in the maternal plasma compartment are in complete equilibrium with the milk compartment. There might be more or less in the milk compartment, but they are still in equilibrium.

B. The chemistry of drug transfer into human milk is largely a function of the chemical structure of the drug.[1]
   1. Lipid solubility is a factor in the drug's transfer into the milk. In general, the more lipid soluble a drug is, the greater the likelihood it will penetrate the alveolar compartment. However, many lipid-soluble drugs have high volumes of distribution, which generally means they will be sequestered in peripheral compartments, such as adipose tissue, brain, and other lipid-rich compartments. This

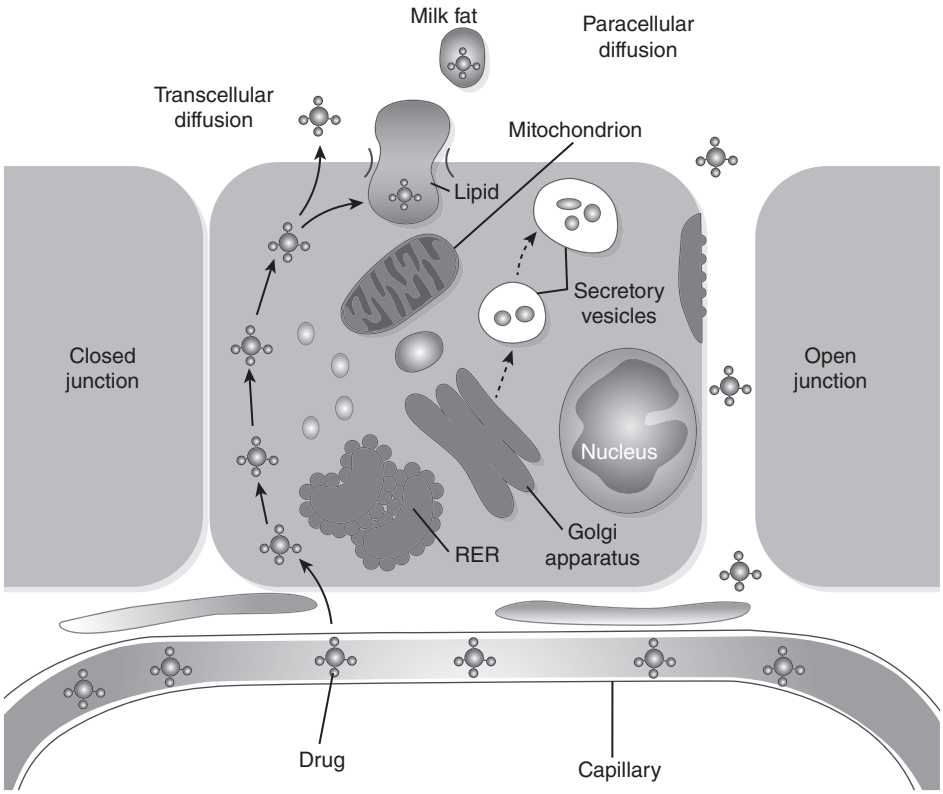

FIGURE 5-1 Alveolar cells during first four days postpartum.

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may actually reduce drug levels in milk because the drug is removed from the plasma compartment and deposited in the peripheral compartment, and thus the drug is shunted away from the milk compartment.

2. The acid-base dissociation constant (pKa) of a drug determines its likelihood of being trapped in the milk compartment, which is called ion trapping. Drugs with a pKa higher than 7.2 may be trapped in the alveolar milk and be unable to exit successfully. This is rarely important clinically.[2]
3. The molecular size of the drug largely determines its transfer into human milk. Without exception, the higher the molecular weight of the drug, the less enters the milk compartment. Drugs greater than 800 daltons have great difficulty attaining clinically relevant levels in milk. In essence, they simply leak into milk through pores that are open due to the loss of a lactocyte or through gaps between cells. Drugs that have large molecular sizes (25,000–200,000 daltons) are virtually excluded from milk in clinically relevant amounts. This includes drugs such as heparin, insulin, interferons, low-molecular-weight heparins, most new biological drugs, and many more.
4. All drugs must attain certain levels in the plasma compartment before they can enter the milk. At present, we know of no other way for drugs to enter milk without first transferring from the plasma. Thus, if a drug does not produce clinically relevant levels in the plasma, it is unlikely to be present in the milk.
5. The volume of distribution of a drug determines its ability to stay in the plasma compartment. Drugs with high volume of distribution are easily transferred out of the plasma to other deep compartments, such as adipose tissue, muscle, and brain.
6. Drugs with high protein binding are largely sequestered in the plasma and have great difficulty entering the milk. Nonsteroidal anti-inflammatory drugs (NSAIDs) are classic examples, with greater than 95 percent protein binding and low levels in milk. Warfarin, with more than 99 percent binding in the plasma compartment, is unable to enter milk at all.
7. The bioavailability of a medication is a measure of how much medication reaches the plasma. Some drugs are destroyed in the gastrointestinal (GI) tract (e.g., proteins, peptides, and aminoglycosides).

BOX 5-1 Relative Infant Dose

$$RID = \frac{Dose.infant\left[\frac{mg/kg}{day}\right]}{Dose.mother\left[\frac{mg/kg}{day}\right]}$$

Dose.infant = dose in infant per day
Dose.parent = dose in mother per day

Others are not absorbed in the small intestine (e.g., vancomycin). Some are significantly metabolized in the gut wall (e.g., domperidone). Regardless, the lower the bioavailability of the drug, the less is transferred into milk. Thus, we prefer drugs with low oral bioavailability.

8. In general, drugs with longer half-lives may build up in the milk production simply because their presence in the plasma is extended, leaving more time for some of the drug to enter the milk.

C. The milk-to-plasma ratio is a useful tool to evaluate the relative concentration of medication in the plasma, compared to the parental milk compartment.
   1. Drugs with a high milk-to-plasma ratio enter milk easily, while drugs with low milk-to-plasma ratios are less able to enter the milk compartment.
   2. In the case where a medication has a high milk-to-plasma ratio (e.g., 5) and an extremely low maternal plasma level, then five times a very low level is still very low (e.g., bupropion).
   3. Unless a great deal is known about the plasma level, the milk-to-plasma ratio might give the clinician the wrong impression. It is therefore recommended that the milk-to-plasma ratio not be used clinically.

D. The relative infant dose (RID) is perhaps the most important clinical parameter to determine the safety of a drug entering the milk.
   1. To calculate the actual dose (D_{inf}) received by the infant, you must know the actual concentration of medication in the milk and the volume of milk that is transferred.
      a. Published studies of many drugs provide the peak concentration (C_{max}) or the average concentration (C_{av}) for the drug.
      b. More recent studies[2] calculate the area under the curve value for the medication or C_{ave}. This methodology accurately estimates the average daily intake by the infant and is much more accurate than the C_{max} estimates.
   2. Ultimately, the simplest method for determining the safety of a medication is to relate the weight-normalized dose to that used during therapy in infants where specific data is available. For example, if the normal dose of a drug that an infant would receive is 10 mg/kg/day, and the infant is receiving 1 mg/kg/day via milk, then you can estimate that the dose is 10 percent of the clinical dose.
   3. The volume of milk ingested is highly variable and depends on the age of the infant and the extent to which the infant is exclusively breastfed. Many clinicians use 150 ml/kg/day to estimate the amount of milk ingested by the infant. However, the most useful and accurate measure of exposure is to calculate the RID (see **BOX 5-1**).
   4. This value is generally expressed as a percentage of the maternal dose. It provides a standardized method of relating the infant's dose to the maternal dose. One recommendation for full-term infants is that an RID of greater than 10 percent should be the theoretical level of concern for most medications.[3] Nevertheless, the 10 percent level of concern is relative, and each situation should be evaluated individually according to the overall toxicity of the medication.
   5. In preterm infants, this level of concern may require lowering the dose appropriately, depending on the medication. It should always be remembered that many neonates may have been exposed in utero and that in utero exposure may be an order of magnitude greater than that received through the milk. Thus, infants who were exposed in utero to methadone go through significant withdrawal upon delivery, even with breastfeeding.

II. Maternal Factors That Affect Drug Transfer

A. Determine the dose of medication by considering the postpartum interval.
   1. At 2 to 4 days postpartum, the dose the infant receives is minimal because the volume of colostrum is minimal (30 to 60 mL/day).
   2. If the infant is 2 weeks to 6 months old, the clinical dose of the drug may be significant because the volume of milk is high. Thus, more caution is required in infants during this stage of development.
   3. At 12 or more months postpartum, the volume of milk is much lower, so the amount of the drug transferred to the infant is lower.
   4. As the infant matures, the ability to metabolize and excrete medications increases. The infant's metabolism becomes highly functional at 9 to 12 months, and infants can adequately handle small loads of drugs through milk.

B. The maternal dose of drug can vary enormously. If the maternal dose is excessively high, use caution in recommending breastfeeding.

C. Drugs with sustained release formulations change the overall plasma half-life of the drug. More caution is recommended with these formulations because plasma and milk levels may be higher and sustained over longer periods, and the clinical dose transferred to the infant may be higher.

D. Dosing intervals of various medications can provide relatively high plasma levels as the drug is absorbed and reaches a peak in the plasma.
   1. Breastfeeding at the peak may produce higher milk levels.
   2. In these situations, and for drugs with a short half-life, it may be possible to breastfeed, take the medication, and avoid breastfeeding at the peak.
   3. This strategy is ideal for drugs such as penicillin antibiotics, isoniazid, and hundreds of other drugs with a short half-life (1 to 4 hours). It generally will not work for drugs with a half-life longer than 4 hours.

E. The oral bioavailability of the drug largely determines the plasma levels and the overall risk to the breastfed infant. Determine whether the dose of medication is actually absorbed orally.

F. Many topical preparations are not absorbed transcutaneously, and pose no problem.

G. Many oral preparations are poorly absorbed from the GI tract, so the plasma levels are significantly lower. These drugs are often not a problem.

H. Hair dyes, most topical creams, drugs such as vancomycin, and dozens of other drugs are poorly absorbed orally and pose little risk to a breastfed infant.

I. Most new biological drugs, such as those used in Crohn's disease, ulcerative colitis, and other syndromes, are monoclonal antibodies (IgG) and thus are more than 150,000 daltons in size. Due to their size, they have consistently been found to produce low milk levels. Further, they are unlikely to be absorbed orally in the GI tract due to the many proteases that break down proteins.

J. Most asthma medications are inhaled; therefore, the level of medication in the plasma level is virtually nil, and it will not likely appear in the milk. Almost all inhaled medications are designed to deliver the drug directly to the pulmonary tissues, and most of these medications are designed to not be absorbed orally or taken up by the liver on the first pass.

III. Predicting Risks of Medications to the Infant

A. Risk factors for an infant depend on several factors.
   1. An infant's metabolic status determines the risk of a negative drug effect.
      a. Low risk: Generally older infants (6 to 18 months) who can metabolize and handle drugs efficiently
      b. Moderate risk: Infants younger than 4 months who have additional risk factors, such as complications from delivery, GI anomalies, hepatitis, or other metabolic problems
      c. High risk: Unstable neonates, preterm infants, or infants with poor renal function
   2. Compare the milk dose with existing pediatric dosing.

3. If the milk levels are known, compare the normal oral dose used in the infant with that transferred via milk. This assessment will provide insight into the risk posed by the level of drug in the milk.
4. Assess if the medication is orally absorbed by the infant. If not, the risk is minimal.

B. Medications with local GI effects can impact the breastfeeding infant.
1. Local effects in the GI tract have been known for many years.
   a. Changes in gut flora and diarrhea have been reported following the use of antibiotics. Generally, this is self-limiting and is not a major problem.
   b. The chronic use of various anticholinergic drugs (e.g., amitriptyline and atropine) and opiates could induce severe constipation. Similar effects are found in adults who use these and other constipating drugs.
2. Breastfeeding should proceed with caution following the use of highly potent or toxic drugs.
   a. In general, the higher the toxicity of the drug, the greater the risk with breastfeeding.
   b. Breastfeeding in mothers using anticancer, antimetabolite, and other highly noxious drugs should follow guidelines for pumping and discarding contaminated milk for five to seven half-lives.[1] This milk cannot be saved, stored, or fed to an infant.

C. Radioactive drugs should be closely evaluated prior to using milk that is contaminated with these substances.
1. Radioactive iodine (I-131) transfers readily into human milk (approximately 27 percent of the maternal dose).[4] Individuals who are planning treatment with this isotope should discontinue breastfeeding and cease lactation prior to its use to prevent high radiation exposure to breast tissues.
2. Close contact with infants or adults should be avoided for up to 10 days after treatment. Additionally, I-131 is highly dangerous to infants, and precautions are mandatory if it is used during breastfeeding.
3. Other isotopes, such as technetium-99, can be used relatively safely.
   a. Although some agencies may not recommend interrupting breastfeeding, technetium-99 has a brief half-life of only 6 hours.
   b. In most cases it is possible to interrupt breastfeeding and use expressed milk for a brief period. Therefore, the recommendation to withhold breastfeeding for 24 hours is a conservative option.
   c. Pumped milk can be stored for 2 to 4 days and used later because the radioisotope will have completely decayed by then and poses no risk.
4. Other radioisotopes may pose some hazard. The InfantRisk Center at Texas Tech University (http://www.infantrisk.com/) can provide recommendations and describe known hazards posed by other radioisotopes.

D. Radiocontrast agents used in CT scans pose little risk to breastfed infants.
1. These agents consist of covalently bound iodine molecules, which are largely unable to decouple from the main carrier molecule; thus, the drug is rapidly cleared from the maternal plasma compartment. As a group, radiocontrast agents are virtually unabsorbed after oral administration (less than 0.1 percent).
   a. Many of these contrast agents have a brief half-life of 1 to 2 hours, and the estimated dose ingested by the infant is negligible.[5] They can even be used intravenously in infants.
   b. Although most package inserts suggest that an infant be removed from breastfeeding for 24 hours, no untoward effects have been reported with these products in breastfed infants.[5]
2. The iodine in these chemical radiocontrast agents is transported in limited amounts to human milk and poses little or no risk to a breastfed infant. The amount of free iodine may be enough to alter a thyroid scan.
3. Gadolinium-containing radiocontrast agents used in MRIs do not readily transfer into human milk[5] (gadolinium is a heavy metal). However, there has been recent concern that a gadolinium ion can decouple from these contrast agents and build up in the brain of adults. At present, we do not know if this produces untoward complications in humans or if it enhances the transfer of gadolinium agents into human milk. In one recent study, no gadolinium deposition occurred in children after repeated exposure to gadolinium-containing radiocontrast agents.[6]

E. Drugs with limited oral bioavailability may or may not be used in breastfeeding infants. Some drugs (e.g., doxorubicin and methotrexate) that are sequestered in the GI tract of the infant could pose severe hazards. Thus, breastfeeding following the use of noxious, particularly anticancer, drugs is not recommended until they have been eliminated from the maternal circulation.

IV. Clinical Implications of Drug Excretion during Lactation

A. The clinical implications of excreting common drugs during lactation include the following:
   1. Acetaminophen: Acetaminophen is approved for use in infants, so there is little concern about the use of this product during lactation. Monitor that the dose is not too high or prolonged. Avoid breastfeeding with excessively high or prolonged dosing.
   2. Aspirin: In low doses, aspirin poses little risk to a breastfed infant. A brief waiting period of 2 hours would likely remove any risk, although this is probably unnecessary. Recent data suggests that doses of 81 mg and even 325 mg are not detectable in human milk immediately following their use.[7] Aspirin is removed from the portal circulation in the gut by the liver before it reaches systemic levels.
   3. Ibuprofen: The RID is very low.[8] The delivered drug is far below the FDA recommended dose that can be directly given to infants.
   4. Celecoxib: The RID is low in short-term use, but chronic use may be problematic.[9]
   5. Diphenhydramine: This antihistamine is used for allergic conditions. It is also used as a sleep aid and as an antiemetic agent to prevent motion sickness.
      a. Small but unreported levels are thought to be secreted into milk. Following an intramuscular (IM) dose of 100 mg, drug levels in milk were undetectable in two individuals, and they ranged from 42 to 100 μg/L in two subjects.[10] Although these levels are low, this sedating antihistamine should be used only for a short duration during lactation.
      b. Nonsedating antihistamines are generally preferred.
      c. There are anecdotal reports that diphenhydramine suppresses milk production. There are no data to support this theory.

B. The clinical implications of vaccine excretion during lactation include the following:
   1. As a general rule, vaccines are safe while breastfeeding.
   2. The yellow fever vaccine is not recommended for use while breastfeeding. However, according to Centers for Disease Control and Prevention recommendations, all persons aged 9 months and older who are travel to or live in areas of high yellow fever transmission should be vaccinated. In addition, it is preferable to avoid vaccinating during lactation when infants are less than 9 months old. However, if travel is unavoidable to an endemic area or an area where the risk of exposure to the yellow fever virus is high, the potential benefits of the vaccine outweigh the potential risks, and immunization should be considered.[11]

C. The clinical implications of antibiotic and antiviral drug excretion during lactation include the following:
   1. Tetracyclines:
      a. The transfer rate of tetracycline antibiotics is very low; however, its absorption may be significant over time.
      b. The short-term use of these compounds for up to 3 weeks is permissible and suitable for the treatment of various infections.
      c. Long-term use, such as for acne, is not recommended during lactation due to the possibility of dental staining in the infant and reduced linear growth rate.
   2. Acyclovir:
      a. Acyclovir is used to treat herpes simplex virus infections, varicella zoster, and other viral infections.
      b. There is almost no percutaneous absorption following topical application, and the plasma levels are undetectable. Therefore, there is no risk in breastfeeding unless the herpetic lesion is on the breast and comes into direct contact with the infant.
      c. Acyclovir levels in milk are reported to be 0.6 to 4.1 times the maternal plasma levels.[12] The maximum ingested doses were calculated to be 1,500 μg/day, assuming a 750 mL milk intake.
      d. An additional study measured milk levels following maternal intake of 200 mg five times daily, and the average milk concentration was 1.06 mg/L.[13]
   3. Penicillins:
      a. Many penicillins have been studied, and are proven to be safe during lactation. Six mothers taking amoxicillin 1 gram orally were studied, and the levels in milk were 0.68 to 1.3 mg/L. This amount is less than 0.5 percent of a typical infant dose of amoxicillin.[14]

b. Ampicillin has been well studied and found to have a RID of 0.2 to 0.5 percent, with the highest reported milk level of 1.02 mg/L in a patient receiving 700 mg three times daily. Ampicillin is commonly used in neonates with no pediatric concerns.[15]
c. It is believed that penicillins can be safely used while breastfeeding.

4. Cephalosporins:
   a. Cephalexin is a commonly used first-generation cephalosporin antibiotic.
   b. Only minimal concentrations are secreted into human milk. Following a 1 gram maternal oral dose, milk levels at 1, 2, 3, 4, and 5 hours were 0.20, 0.28, 0.39, 0.50, and 0.47 mg/L, respectively.[14] These levels are too low to be clinically relevant.
   c. Cefotetan is a third-generation cephalosporin that is poorly absorbed orally and is typically used IM or intravenously (IV). The drug is distributed into human milk in very low concentrations with an RID of 0.02 to 0.03 percent.[16]
   d. The cephalosporins have been used in breastfeeding without any safety concerns.
5. Fluoroquinolones:
   a. Studies of the new fluoroquinolones suggest that ofloxacin (and its derivatives) concentrations in milk are probably lowest.
   b. Ciprofloxacin concentrations in human milk vary over a wide range but are generally quite low (2.1 to 2.6 percent).[17,18]
   c. Ciprofloxacin use in pediatrics has increased in recent years, and numerous studies indicate little risk from exposure.
6. Metronidazole:
   a. Following an oral dose of 400 mg three times daily, the maximum concentration in milk was reported as 15.5 mg/L.[19] The reported RIDs were moderate, approximating 10 to 13 percent of the maternal dose.
   b. Some reports suggest that a metallic taste is imparted to the milk.
   c. High oral doses, such as 2 g for the treatment of trichomoniasis, may produce high milk levels. At this dose, a brief interruption of breastfeeding is recommended for 12 to 24 hours.
7. Macrolides:
   a. New data suggests that the use of erythromycin early in the postnatal period increases the risk of hypertrophic pyloric stenosis.[20]
   b. For this reason, azithromycin or clarithromycin are the preferred choices during the postnatal period.
8. Fluconazole:
   a. A significant transfer (RID = 12 percent) into the milk has been proven safe and is far less than clinical doses that are commonly prescribed for infants.
   b. Although there is some risk of elevated liver enzymes, none have been reported following exposure to fluconazole in milk.
9. Antifungals:
   a. Topical antifungals, such as nystatin or miconazole, are often used to treat candidiasis and are considered safe as long as minimal amounts are applied to limit oral absorption by the infant.
   b. Clotrimazole has been implicated in contact dermatitis and should be avoided if possible.[21]

D. The clinical implications of selective serotonin reuptake inhibitor (SSRI) excretion during lactation include the following:
1. Antidepressant therapy in breastfeeding women is strongly recommended for maternal depression. Interestingly, this is the drug class that is most often studied in lactation. Clinical studies of sertraline and paroxetine clearly suggest that the transfer of these agents into milk is quite minimal.[22,23]
2. Neonatal withdrawal symptoms are commonly reported in 30 percent or less of infants exposed to certain SSRIs during pregnancy. Early postnatal symptoms consist of poor adaptation, irritability, jitteriness, and poor gaze control in neonates exposed to paroxetine, sertraline, and, less so, fluoxetine.
3. In contrast to transfer across the placenta, the SSRI levels in milk are very low, and uptake by the infant is even lower. There is strong evidence of safety while using this family of drugs during breastfeeding.[22,24,25]

E. The clinical implications of anticoagulant medication excretion during lactation include the following:
   1. Warfarin:
      a. Warfarin is highly protein bound, and very little is secreted into human milk.
      b. In one study, two patients were anticoagulated with warfarin. No warfarin was detected in the infants' serum, and no changes in coagulation were detected.[26]
      c. In another study of 13 mothers using warfarin, less than 0.08 μmol/L was detected in milk, and no warfarin was detected in the infants' plasma.[27]
      d. Supplementation with vitamin K will negate any small amount of warfarin that a breastfed infant might receive.
   2. Enoxaparin:
      a. Enoxaparin is a low-molecular-weight heparin used for anticoagulation.
      b. In one study of 12 women using 20 to 40 mg daily, no change in anti-Xa level was noted in any of the 12 breastfed infants.[28]

F. The clinical implications of antiseizure medication excretion during lactation include the following:
   1. Lamotrigine:
      a. Lamotrigine is an anticonvulsant used as an antiseizure medication.
      b. In a study of nine breastfeeding mothers at 3 weeks postpartum, the median milk-to-plasma ratio was 0.61, and the breastfed infants maintained lamotrigine concentrations of approximately 30 percent of the maternal plasma level.[29] There is one case report of an infant with severe apnea.[30] The mother was receiving 850 mg/day and breastfeeding. Lamotrigine is extensively used in seizure and bipolar disorders during lactation, with little or no reported complications. If low to moderate doses are used, it has proven safe to use while breastfeeding.[31]
   2. Valproic acid (VPA):
      a. VPA is a popular anticonvulsant used for seizure management.
      b. In one study of 16 patients receiving 300 to 2,400 mg/day, VPA concentrations ranged from 0.4 to 3.9 mg/L. The milk-to-plasma ratio was 0.05 in the study participants.[32]
      c. Most experts agree that the amount of VPA that transfers into milk is very low and that this drug can be used safely while breastfeeding.
      d. However, VPA is a known teratogen, and its use should be restricted in women who may become pregnant or those who are breastfeeding and may become pregnant. If VPA is used, effective birth control is mandatory.
      e. Some VPA will transfer into human milk and could reduce neurobehavioral development in the breastfed infant.[33] Due to the availability of numerous effective anticonvulsants, the use of VPA in breastfeeding women is not recommended unless all other options have been ruled out.
   3. Topiramate (used as an anticonvulsant):
      a. In one study of two women receiving 150 to 200 mg/day at 3 weeks postpartum, the concentration of topiramate in milk averaged 7.9 μM.[34] The absolute infant dose was 0.1 to 0.7 mg/kg/day. The plasma concentrations in the two infants were 1.4 and 1.6 μM, which was 10 to 20 percent of the mothers' plasma level.
      b. Infants should be closely monitored for sedation. Occasional blood level monitoring is recommended.

G. The clinical implications of antihypertensive medication excretion during lactation include the following:
   1. Calcium channel blockers:
      a. Nifedipine is a commonly used antihypertensive.
         i. There are two studies that indicate nifedipine is transferred into human milk in very low levels. Both published studies agree that the level transferred into human milk is of no clinical consequence to infants.
         ii. One study measured milk levels following doses ranging from 10 to 30 mg three times daily. The highest concentration in milk was 53.35 μg/L, measured at 1 hour after a 30 mg dose.[35]
         iii. Another study followed concentrations of nifedipine in human milk 1 to 8 hours after 10 mg doses. The levels varied from less than 1 to 10.3 μg/L in 6 of 11 patients.[36]

b. Nicardipine has been studied in breastfeeding mothers, and the RID was estimated to be 0.07 percent.[37]
c. Calcium channel blockers are considered safe for use in breastfeeding.

2. Beta-blockers:
a. Labetalol is a selective beta-blocker often used as an antihypertensive. In one study of three women receiving 600 to 1,200 mg/day, the peak concentrations of labetalol in milk were 129, 223, and 662 μg/L, respectively.[38]
b. Metoprolol is a cardioselective beta-1 blocker used as an antihypertensive. In a study of three women at 4 to 6 months postpartum who were receiving 100 mg twice daily, the peak concentration of metoprolol ranged from 0.38 to 2.58 μmol/L.[38] The RID is approximately 1.4 percent.[39]
c. Propranolol is a beta-blocker used for hypertension and migraine headaches. In general, the parental plasma levels are very low. One study of three patients revealed that the average milk concentration was 35.4 μg/L after multiple doses.[40]
d. Atenolol and acebutolol are the only beta-blockers that require caution. Case reports describe infants with cyanosis and bradycardia when their mothers were being treated with these two beta-blockers.[41]

3. ACE inhibitors:
a. Captopril is an ACE inhibitor that is used as an antihypertensive. In a report of 12 women treated with 100 mg three times daily, the milk levels were 4.7 μg/L at 3.8 hours after a dose.[42]
b. Lisinopril is commonly used as an antihypertensive, but there is no breastfeeding data for this drug.
c. The concern for this class of drugs is the theoretic risk of an extremely preterm infant being exposed to these medications. In pregnancy, ACE inhibitors are avoided due to known fetotoxic effects. Because the kidney does not fully mature until after birth, there is some concern about potential renal effects of ACE inhibitor exposure through milk in a preterm infant, although this is a theoretical risk.

4. Diuretics:
a. Furosemide is a potent loop diuretic with a 3 hour half-life. It is used extensively in the immediate postpartum period as an antihypertensive and to help remove excess intravascular volume. It is used frequently in neonates in intensive care units and in pediatrics. It has very low oral bioavailability in neonates. Furosemide levels in milk have not been reported.
b. Hydrochlorothiazide is a thiazide diuretic that is often used postpartum for volume control and for hypertension. In one study, a mother received 50 mg every morning, and her milk levels were 25 percent of her plasma levels. This means the infant would receive approximately 50 μg/day, which is not clinically significant.[43]

H. The clinical implications of pain management drug excretion during lactation include the following:
1. Hydrocodone is a narcotic analgesic. Its active metabolite is hydromorphone.
a. Hydrocodone is very effective for the relief of postpartum and postoperative pain, and it is commonly used.
b. In a recent study, hydrocodone and hydromorphone levels were measured in 125 milk samples obtained from 30 women receiving 0.14 to 0.21 mg/kg/day. The authors concluded that a fully breastfed infant would receive about 2.4 percent of the maternal hydrocodone dose.[44]
c. Milk samples in two of the studied women were very high, with a hydromorphone-to-hydrocodone ratio of 2.8 and 3.1. It is possible that these women metabolized the drug faster, so the risks of opiate exposure to their infants were higher.
d. Overall, it is recommended that hydrocodone is safe if used for short time frames and less than 30 mg daily.

2. Codeine is a mild opiate analgesic, and its metabolite is morphine (approximately 7 percent).
a. The amount of codeine secreted into milk is low.
b. Four cases of neonatal apnea have been reported following maternal administration of 60 mg of codeine every 4 to 6 hours.[45]

c. An infant death has been reported following maternal use of codeine. The genotype of this mother indicated that she was an ultrarapid metabolizer of codeine.[46]
d. Caution should be used with codeine. Numerous national drug advisory groups around the world, including the FDA, have recommended that it no longer be used during lactation.

3. Morphine is a potent analgesic.
   a. In a group of five lactating women, the highest morphine concentration in milk following two epidural doses was only 82 μg/L at 30 minutes.[47] The highest milk level following 15 mg IV or IM administration was only 0.5 mg/L, and it dropped to almost 0.01 mg/L in 4 hours.
   b. In another study of women receiving morphine via patient-controlled analgesia (PCA) pump for 12 to 48 hours postpartum, the concentration of morphine in milk ranged from 50 to 60 μg/L.[48]
   c. The oral bioavailability of morphine is low because it is rapidly cleared by the liver; however, the clearance of morphine is slower in an infant less than 1 month old.
   d. Morphine can be safely used for short time frames and if the infant is monitored for signs of increased sedation or poor feeding.
4. Hydromorphone is a potent semisynthetic narcotic analgesic that is approximately 7 to 10 times more potent than morphine, but it is used in equivalently lower doses.
   a. In a group of eight women who received 2 mg of intranasal hydromorphone, the milk levels ranged from about 6 μg/L at 1 to 1.5 hours to 0.2 μg/L at 24 hours (estimated from a graph). The observed milk-to-plasma ratio averaged 2.56, and the half-life of hydromorphone in milk was 10.5 hours. The authors of this study estimated an RID of 0.67 percent.[49]
   b. If a maternal dose were 4 mg of hydromorphone every 6 hours, the infant would ingest about 0.002 mg/kg/day, or 2.2 μg of the 4 mg taken.[49] This is significantly less than the clinical oral dose recommended for infants and children with pain (0.03 to 0.06 mg/kg/dose every 4 hours as needed).
5. Tramadol is used as an analgesic and closely resembles opiates but has a reduced addictive potential.
   a. In a study of 75 mothers who received 100 mg every 6 hours after cesarean section, milk samples were taken on days 2 to 4 postpartum in transitional milk. The estimated absolute and relative infant doses were 112 μg/kg/day and 30 μg/kg/day for rac-tramadol and its desmethyl metabolite. No significant issues arose with infants exposed to these doses in breastmilk.[50]
   b. Although the FDA no longer recommends this drug during lactation, there are no reported complications in any breastfed infant.

I. The clinical implications of excreting drugs of abuse during lactation include the following:
1. Alcohol:
   a. The consumption of ethanol has been shown to inhibit oxytocin release and decrease milk delivery to the infant.[51]
   b. An average-sized woman will metabolize a standard drink (14 g pure ethanol) in about 2 hours. Thus, a waiting period of 2 hours per drink consumed is recommended.[52]
2. Tobacco:
   a. Studies show a linear relationship among smoking in the breastfeeding parent, nicotine levels in the milk, and urine cotinine (nicotine's main metabolite) levels in the breastfed infant.
   b. Second-hand smoke can contribute to otitis media, respiratory tract infections, sudden infant death syndrome, and asthma in the infant.
3. Marijuana or cannabis:
   a. Research is limited concerning the concentration of marijuana in milk. The milk levels are reportedly low, but the milk-to-plasma ratio has been reported as high.
   b. Thus far, no study has demonstrated measurable clinical effects in infants exposed to marijuana.
   c. Significant evidence has begun to emerge suggesting that exposure to THC in pregnancy, or chronic use in adolescence and early adulthood, may result in changes to the endocannabinoid system in the brain, which regulates mood, reward, and goal-directed behavior.

d. Adverse neurobehavioral effects have not yet been demonstrated in infants exposed to THC. Mothers who deliver infants who are drug-screen positive should be advised to discontinue the use of cannabis, but they should be permitted to continue breastfeeding.
e. Current studies are underway that may alter these recommendations. Unpublished data from our laboratories suggest that the RID for smoked marijuana is approximately 2.4 percent.

4. Opiate drugs:
   a. Opiate medications are commonly used in breastfeeding mothers, but these drugs must be used with caution because respiratory depression can occur with high doses.
   b. Morphine is generally considered the best choice because it is poorly absorbed in infants.
   c. Opiate derivatives, such as heroin, fentanyl, sufentanil, and meperidine, should be avoided when used at high doses in abusive situations.
5. Cocaine:
   a. There are no available data on the transfer of cocaine into human milk.
   b. Due to its chemistry, cocaine levels in milk may be excessive, and users should avoid using cocaine while breastfeeding.
   c. Studies with exact estimates of cocaine transmission into breastmilk have not been reported due to the difficulty of determining maternal dose and timing of milk samples. However, case reports demonstrating transmission of this drug and its metabolites into milk do exist.
   d. In the first case, a mother reported using 0.5 g of cocaine intranasally over 4 hours, and she breastfed her infant five times during this period.[53] The infant became irritable; had vomiting, diarrhea, and dilated pupils; and had difficulty focusing on the mother's face. On examination, the infant was tremulous, irritable, tachycardiac, tachypneic, and hypertensive with an increased startling response. The infant's pupils were dilated with a poor response to light, and the reflexes were increased.
   e. A waiting period of 24 hours, following the use of cocaine is recommended, during which milk is pumped and discarded.[1]
   f. Drug screens will remain positive for more than 5 days after the use of this drug.

J. The clinical implications of biological drug excretion during lactation include the following:
1. Many new biological drugs are, in most cases, derived from the human immune globulin IgG_1, although some are derived from IgG_4. These drugs are used to treat syndromes such as multiple sclerosis, arthritis, Crohn's disease, ulcerative colitis, and cancer in a new era of using immune therapy to combat disease.
2. All these drugs consist of a specially modified IgG molecule, which on average weighs about 150,000 daltons. These compounds leak into milk at low levels through random gaps in the alveolar apparatus.
3. At present, numerous studies suggest that milk levels are exceedingly low and that any of the drug that is present in milk is probably not orally absorbed because the molecules are rapidly denatured by gastrointestinal proteases.[54-56]
4. It currently appears that the benefits of breastfeeding and enhanced maternal health greatly outweigh any potential side effects from this class of medications.

V. Galactagogues That Stimulate Milk Production

A. Herbal drugs:
1. Fenugreek is the most commonly used herb for increasing milk production.
2. There is little hard evidence that herbal preparations may increase milk production. The most recent placebo-controlled study published as an abstract in 2011 suggested that fenugreek had no effect on either prolactin levels or milk volume.[57] This study included 26 mothers of preterm infants that took 1,725 mg fenugreek three times a day for 3 weeks.
3. Although no adverse effects are noted, herbal products are not controlled by the FDA, so the quality and consistency of products are unknown and may put the mother or infant at risk of unknown adverse effects.
4. Fenugreek is not recommended to improve milk production.

B. Domperidone:
   1. Numerous studies over the past 30 years have documented that domperidone is a major galactagogue.
   2. Formerly introduced as a gastrokinetic drug, domperidone stimulates prolactin production to a major degree. As such, in women who are hypoprolactinemic while breastfeeding, it will increase milk synthesis and production rapidly and efficiently.
   3. More than a dozen studies have clearly documented that domperidone will increase milk production in some women.[58-64]
      a. This occurs only if prolactin levels are low (less than 79 ng/mL). It will not work when prolactin levels are high. Thus, determining the prolactin level is a major requirement before instituting therapy with this drug.
      b. Patients should be advised to breastfeed, then after 2 hours a plasma sample should be taken to determine the prolactin level. At 2 hours, the peak will have been avoided, and the trough level will be present in the plasma. If this level is low (10 to 50 ng/mL), domperidone will probably increase milk production significantly.
   4. Following prolonged therapy, a withdrawal period is recommended in most cases to prevent a precipitous drop in prolactin levels. In a recent study to determine the effect of domperidone withdrawal on subsequent milk production kinetics, 25 women who initially received domperidone (20 mg four times daily) were gently withdrawn stepwise over a period of 2 to 4 weeks, from 20 mg four times daily, to 10 mg four times daily, to nil.[65] In the study, 23 of 25 cases (93 percent) reported no significant increase in formula use after stopping domperidone. Normal infant growth was reported in all cases.
   5. Domperidone is known in some rare cases to induce arrhythmias.[66,67] This occurs primarily in older males and in individuals who are proarrhythmic. Do not use domperidone at doses higher than 20 mg three times daily. As the dose escalates, the risk of arrhythmias increases.

C. Metoclopramide:
   1. Metoclopramide, a dopamine receptor blocker, has multiple functions and is primarily used for increasing the tone of the lower esophageal sphincter in patients who have gastroesophageal reflux. It is sometimes used during lactation to stimulate prolactin release from the pituitary gland and enhance milk production.[68,69]
   2. Although metoclopramide is well known to increase the release of prolactin, similar to domperidone, it is fraught with side effects, such as depression, although some patients have used it successfully for months. The FDA has warned that therapy longer than 3 months may be associated with tardive dyskinesia and extrapyramidal symptoms. The exposure should be limited to no more than 1 month.
   3. The general recommendation is to taper the dose. One possible regimen is to decrease the dose by 10 mg per week.

Key Points from This Chapter

A. During the colostral period, the transfer of drugs into milk is higher. However, the total dose transferred is lower because of the limited volume of colostrum during the first few days.
B. Medications enter the milk compartment only from the mother's blood. If the drug is not absorbed into the plasma compartment, it does not enter the milk compartment.
C. Although all drugs enter milk, most drugs enter at clinically insignificant levels. Determine the levels in milk, the Relative Infant Dose (RID), and the lactation risk category.
D. Recommend discontinuing breastfeeding if the drug poses a major risk to the infant. This includes high doses of sedative drugs, opiate narcotics, radioactive agents, anticancer drugs, and other noxious drugs.
E. Be cautious of high vitamin doses. Do not use high doses of iodine. Advise moderation in the use of any drug.
F. Keep breastfeeding parents healthy to avoid the need for medicinal treatment. Make sure they take care of their health, both mental and physical. If a health condition requires treatment, carefully choose the drugs to treat it.

CASE STUDY

A 31-year-old mother delivered vaginally at 28 weeks gestation due to preterm labor and bleeding and a presumed placental abruption. The infant weighed 850 grams, had Apgar scores of 5 and 8, and a pH of 7.1. At delivery, the infant was intubated and transferred to the neonatal intensive care unit (NICU). A review of the prenatal records indicated a history of chronic back pain since a car accident 3 years before. At delivery, the mother was reportedly using 130 mg oxycodone daily, 600 mg gabapentin three times daily, and cyclobenzaprine 10 mg three times daily for chronic pain syndrome. The mother was stable in the recovery room and requested to breastfeed.

The mother's oxycodone dose is exceedingly high, and the gabapentin and cyclobenzaprine doses are at the highest levels. The infant will undoubtedly go through withdrawal over the next few days. It is likely that the amount of these agents in the milk is sufficient to allay the severity of withdrawal, but only to a limited degree. New data suggest that adding gabapentin or pregabalin to opiate therapy greatly exaggerates withdrawal symptoms in infants.

The fact that this infant was placed in the NICU is beneficial because respiratory function, blood pressure, and other biological functions can be closely monitored by the NICU staff, both during withdrawal and before discharge to home while breastfeeding continues. It is possible that this infant can be fed expressed milk or can breastfeed later, with the recommendation that the maternal doses of these medications be reduced significantly over the ensuing weeks. Had this infant been born at full term and not admitted to the NICU, breastfeeding after hospital discharge would require continued monitoring at home.

Questions

1. If the mother had undergone general anesthesia for an emergent cesarean section, and the medications used on induction included propofol and succinylcholine, at what time post procedure would it be safe for her to breastfeed?
2. If the mother had a seizure in the recovery room and was placed on a magnesium infusion for seizure prophylaxis, would it be safe for her to breastfeed the infant?
3. What if the mother developed acute shortness of breast/chest pain during her postpartum course and there was concern for a pulmonary embolism? She undergoes a CT angiogram with IV contrast to rule out pulmonary embolism. Is there any contraindication to breastfeeding with contrast agents?
4. What if a urine toxicology screen was sent on the mother to rule out illicit drug use and the urine toxicology indicated use of cannabis products? Would marijuana use change your counseling on safety of breastfeeding?

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Additional Resources

InfantRisk Center. http://www.infantrisk.com.
Motherisk. Pregnancy and Breastfeeding Safety Guide. http://www.motherisk.org/women/contactUs.jsp.
National Institutes of Health. LactMed: A Toxnet Database. https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm.