

# Drugs & Breastfeeding: An Update

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## GOALS AND OBJECTIVES

### Goals:

To provide the pharmacist with information regarding the elimination of drugs in breast milk.

### Objectives:

After completing this article, the pharmacist should be able to:

1. Understand the production and composition of breast milk.
2. Describe factors that influence drug passage into milk.
3. Discuss the mechanisms for predicting which drugs would be eliminated in breast milk.
4. List various alternative mechanisms for using drugs in the lactating woman.

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There has been increased interest in the past two decades regarding drug use during breastfeeding. This has evolved from the concerns regarding the elimination of drugs in breast milk as well as the increasing number of women who nurse their infants.

Although the information regarding drug elimination in breast milk has increased dramatically, there is still not a wealth of reliable information and it is difficult to obtain subjects to perform research. Computer models are useful and often provide valuable information, but limitations remain regarding the predictability of drug elimination in breast milk.

### **Structure of the Normal Breast**

The fully developed female breast is composed of connective tissue, adipose tissue, and functional glandular epithelium. The glandular epithelium is organized into approximately 20 lobes, each of which is subdivided into lobules that are supported by the surrounding connective tissue. The lobules consist of clusters of secretory epithelial cells arranged into milk-producing alveoli. These alveoli open into small alveolar ducts, also composed of epithelium. Numerous alveolar ducts join to form larger interlobular ducts, several of which drain into a lactiferous duct. Each lobe of the mammary gland is drained by a single lactiferous duct that emerges at the nipple. A lactiferous duct has an enlarged portion, the ampulla or sinus, that is located just beneath the surface of the nipple and that serves as a reservoir for milk in the lactating gland. Drugs cross from the blood in the capillary beds through the alveoli and into the lactiferous ducts.

### **Composition of Milk**

The composition of milk is determined by the mammary gland. The milk occurs in three forms which are known as colostrum, transitional milk and mature milk. The colostrum is a transudate consisting primarily of serum albumin and is a precursor which usually lasts less than four days. Transitional milk is produced during the first week of breastfeeding and lasts for several weeks. It has less fat and sugar initially, but during the several week period, it becomes mature milk and these values usually increase. Mature milk is usually established by the end of the first month of lactation. Typically, it contains slightly more than one percent protein, 2 percent to 6 percent fat, and approximately 7 percent lactose. The composition of milk at the beginning of the feeding is highest in protein and lowest in fat. However, these values are reversed by the end of the feeding.

### **Milk Production**

Numerous factors may alter milk production. Prolactin is present in high concentrations during pregnancy and breastfeeding, but low concentrations after birth in the absence of breastfeeding. Estrogen and progesterone are assumed to inhibit lactation, but low concentrations, such as that found in oral contraceptives, do not appear to have

a major impact. Emotional changes, particularly those that result in high levels of catecholamines, can inhibit milk expression. Medications may also alter milk expression. In general, the quantity of milk produced will depend in a large part on the demands of the infant. During feeding, milk stores will be depleted, but are usually easily replenished because this is a discontinuous process.

### **Drug Passage into Milk**

Unless there is contrary information, drugs will pass into milk. In many instances, the quantity is not sufficient to illicit a clinical effect.

Drugs pass into breast milk by passive diffusion down a concentration gradient formed by the nonionized, free drug on each side of the membrane which acts as a semi permeable lipid barrier. Drugs with molecular weights of 200 or less easily pass into breast milk.

The normal pH of blood ranges from 7.35 to 7.45, while that of milk ranges from 6.5 to 7.4. Consequently, milk is typically somewhat acidic relative to plasma. When exposed to body fluids of varying pH values and separated by a membrane, a drug will accumulate in the fluid in which it is most ionized and where it is most soluble. Therefore, in general, basic drugs are excreted in higher concentrations in milk.

Both plasma and milk contain proteins that can bind drugs. However, plasma contains more and a larger amount of proteins, such as albumin, that bind drugs. Therefore, highly plasma protein bound drugs usually remain in plasma and pass into milk in low concentrations. Since milk contains fat, lipid soluble drugs may concentrate in the fat which could result in a significant increase in their concentration in milk. However, although this effect can occur, it does not appreciably alter the total amount of drug reaching the infant.

As mentioned previously, many of these functions are discontinuous processes (i.e., breastfeeding, drug ingestion). Therefore, the interrelationships with regard to drug passage into breast milk will depend somewhat on the quantity of milk available, the half-life of the drug, and/or the processes by which the drug achieves equilibration. These factors, as well as the molecular weight and lipid solubility of the drug, are important in determining the concentrations of the drug in milk and plasma.

### **Predicting Drugs in Breast Milk**

There are numerous factors that can affect the amount of drug that will appear in breast milk. Although the complex pharmacokinetic and computer models that are used today may provide more reliable information, the many variables (i.e., mother, infant, multiple drugs, variability among drugs) that must be considered simultaneously make predictions difficult.

For many years, the milk-to-plasma (m/p) ratio was used

as a predictor. The m/p is derived from the measured drug concentrations in plasma and milk during equilibrium. However, the m/p has been misused in the past and its reliability is inconsistent. There have been several different methods and applications for m/p. However, despite its wide use, the m/p is not a consistent method for predicting drugs in breast milk.

Of paramount importance is the amount of drug the infant would receive in a breastfeeding period. Therefore, estimates of infant dosage are usually more relevant than m/p. The infant dosage can be estimated by measuring the concentration of drug in the milk and determining the usual amount of milk ingested by the infant. Most infants ingest 150 ml/kg/day (variation = 120 ml to 230 ml/kg/day). In addition, the drug concentration in milk is usually linearly related to the maternal dose. Although many of the values in this process are estimates, this procedure appears to be more consistent and provide more relevant information (infant dosage) than m/p. If the dose the infant received can be adequately estimated, then this amount can be compared with the typical pharmacologic dose the infant would receive to determine if there is a significant amount being ingested by the infant.

Theoretically, the elimination of drugs in breast milk is predominately dependent on the following physicochemical factors:

1. pKa or degree of ionization of the drug
2. pH gradient between plasma and milk
3. lipid-water solubility characteristics of the drug
4. concentration gradient of diffusable drug between plasma and milk

The average pH of blood is 7.40 with a range between 7.35 and 7.45. Breast milk, which is considered to be an alkaline substance, is more acidic than blood and has a pH range of 6.5 to 7.4 with an average of 6.8. The pKa of a drug is an index of acidity.

Therefore, compounds with low pKa values are strong acids (pKa=2.5), whereas those with high pKa values are bases. pKa are logarithmic relationships. Each unit change reflects a 10-fold change in concentration.

In most instances, the unionized drug will diffuse across cell membrane barriers much more easily than ionized drugs. A drug with a pKa below the pH of blood will be more ionized in blood than in breast milk. Therefore, acidic drugs are usually less concentrated in breast milk than basic drugs. If the drug is protein bound, it will not diffuse across cell membrane barriers unless an active transport mechanism is involved. In general, unionized nonprotein-bound moderately lipid soluble molecules will diffuse across cell membrane barriers easier than other molecules. In this case, pKa seems to be a major determinant for passage of a drug into breast milk.

Several of these factors can be applied quantitatively to predict the percentage or portion of the drug that is ionized and unionized. This can be accomplished with the

use of the Henderson-Hasselbach equation:

$$\text{pH} = \text{pKa} + \log \frac{\text{ionized}}{\text{unionized}} \quad (1)$$

$$\text{pH} = \text{pKa} + \log \frac{\text{unionized}}{\text{ionized}} \quad (2)$$

Equation (1) is for acidic drugs, while equation (2) is for basic drugs. When a drug is exposed to body fluids of various pH that are separated by a physical membrane (plasma and breast milk), the drug will accumulate in the fluid in which it is most ionized. From equation (1), it can be predicted that the majority of acidic drugs will not be readily ionized in breast milk. Since plasma has a higher pH (7.4) than breast milk (6.8), the acidic drugs will be more ionized in plasma and not readily diffuse across the membrane barrier.

These physicochemical factors provide a rational basis for predicting which drugs should be eliminated in breast milk. However, this does not predict the clinical significance or account for the many variables that can alter the predictions based on physicochemical factors.

#### **Drugs and Breast Milk Elimination**

All drugs should be assumed to be eliminated in breast milk, unless there is clear documentation indicating that this does not occur. However, for the majority of drugs, the amount received by the infant during breastfeeding is not clinically significant.

Most analgesics and antipyretics are eliminated in breast milk in small amounts. Acetaminophen, aspirin, and the NSAIDs are found in small quantities. Ibuprofen has been evaluated and does not appear to have measurable amounts in breast milk in typical doses. The use of narcotic analgesics should be avoided in the nursing mother. Although narcotics are eliminated in breast milk in small amounts, there have been some effects demonstrated by the infant.

Anticonvulsants, such as carbamazepine, ethosuximide, and phenobarbital have produced effects in breastfeeding infants. Valproic acid and phenytoin have not demonstrated clinically significant activity in infants.

Antihistamines should be taken as a single bedtime dose after the last breastfeeding to minimize infant exposure. Cyproheptadine lowers maternal serum prolactin and should be avoided.

Most antimicrobial drugs are eliminated in breast milk in small amounts. However, there are various individual incidences that indicate toxicities that are related to side effects produced by the antimicrobial. In general, long-acting sulfonamides, sulfones, chloramphenicol, amantadine, acyclovir, and metronidazole should be avoided and other antimicrobials should be used with caution.

Women receiving immunosuppressants and/or

antineoplastics should avoid breastfeeding their infants. In many instances, there have been no problems encountered with the use of azathioprine or busulfan in mothers who are breastfeeding. However, the general activity of these drugs indicates that there is potential harm for the infant. Many of the beta adrenergic blocking drugs are eliminated in breast milk in quantities that may produce activity in the infant. However, propranolol, metoprolol, and labetalol appear to be safe to use.

Several antiarrhythmics and hypotensive agents should be used with caution in breastfeeding women. Clonidine and reserpine have demonstrated some activity in infants and should be avoided. Amiodarone appears to have concentrations in breast milk that may produce activity in infants. There are other drugs in each of these groups that are safer alternatives in the breastfeeding woman.

Loop diuretics and longer acting thiazide diuretics may suppress lactation and should not be used in breastfeeding women. The use of low doses of short acting thiazide diuretics appears safe in most instances, but the general structure (i.e., sulfonamide-related) could pose a problem.

Drugs acting in the gastrointestinal tract have various effects on breastfeeding. Laxatives and antiarrheals that are nonabsorbable are considered not to be harmful. However, cimetidine and metoclopramide should not be used in breastfeeding women.

Combination oral contraceptives have suppressed lactation and have rarely produced some activity in infants. However, the lower dose combination products, as well as the progestin products, have not demonstrated any significant problems.

Information on the use of central nervous system drugs, such as psychotherapeutic drugs (e.g., lithium) and sedatives and hypnotics, varies. However, in general, these drugs generally appear in breast milk in amounts that could produce activity in the infant.

It is difficult to determine the effects of using social substances, such as tobacco or alcohol. Excessive quantities of alcohol have produced sedation in the infant. Smoking more than one pack of cigarettes per day has caused nicotine effects in infants. All substances of abuse should be avoided during breastfeeding.

This summary of the various classes of drugs provides a general review of information. However, each drug and particular individual situation must be assessed to determine whether the benefits of using the drug outweigh the potential risks to the infant. Many drugs have not been evaluated or have not been adequately or sufficiently evaluated. Consequently, the recommendations of the manufacturer should provide the information needed to determine appropriate use in breastfeeding women.

#### **Drug Use in The Lactating Mother**

In many instances, the use of drugs in women who are breastfeeding is easily accomplished. However, if therapy

is not necessary, then it is best to withhold drugs. Therefore, any elective therapy should be delayed.

If the lactating mother must consume a drug, she should ingest the medication immediately after nursing. This would provide three or four hours before the next feeding and allow enough time for most medications to be at a relatively low breast milk concentration. If possible, medications should not be consumed one half to one hour prior to breastfeeding the infant. In many cases, the drug would be near peak concentrations at some time during the feeding process. In addition, drugs that do not accumulate in breast milk should be selected when possible.

Other alternatives would be to terminate breastfeeding during therapy, to attempt to have a supply of breast milk available prior to drug therapy, or to alternate breastfeeding and other feeding methods to avoid exposure during peak drug concentrations.

If there are potential problems for the infant and the mother must receive the drug, then breastfeeding may need to be discontinued.

#### **Conclusion**

The use of drugs in women who are breastfeeding their infant is becoming more important as the benefits of breastfeeding have become recognized. Many times, there are therapeutic programs that will allow the mother to continue breastfeeding while receiving drug therapy.

There are many variables to assess in evaluating the use of drugs in breastfeeding infants. Although there is increasing information, guidelines for selecting drugs remain unclear in many instances. Without sufficient data, the manufacturer should provide the information needed to determine the appropriate use of the drug in the breastfeeding infant.

**Table 1**  
**Examples of Drugs and/or Chemicals**  
**That Are Contraindicated During Breastfeeding**

Amantadine  
Aminodarone  
Antineoplastic Agents  
Bromide  
Chloramphenicol  
Cocaine  
Cyproheptadine  
Indandione Anticoagulants  
Iodine  
Metoclopramide  
Radiopharmaceuticals  
Salicylates (In Large Doses)  
Drugs of Abuse

**Table 2**  
**Examples of Drugs and/or Chemicals**  
**That Should Be Used With Caution or Avoided While Breastfeeding**

Acebutolol  
Alcohol  
Antihistamine/Decongestant Combinations  
Benzodiazepines  
Cimetidine  
Clindamycin  
Clonidine  
Contraceptives(Estrogen Containing)  
Cyclosporine  
Ergotamine  
Ethosuxinide  
Fluoxetine  
Lindane  
Lithium  
Methimazole  
Metronidazole  
Nadolol  
Narcotics  
Nicotine  
Nitrofurantoin  
Phenobarbital  
Piroxicam  
Primidone  
Quinolone Antibacterials  
Reserpine  
Sotalol  
Sulfonamides  
Thiazide Diuretics (High Doses)