Maternal Medication, Drug Use, and Breastfeeding

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KEYWORDS

• Breastfeeding • Medications • Infant exposure • Antidepressants • Antipsychotics

KEY POINTS

- Drugs transfer into milk as a function of molecular weight. The higher the molecular weight, the less the drug transfers into human milk.
- Drugs transfer into human milk as a function of the maternal plasma level. The higher the plasma level, the higher the transfer into human milk.
- Drugs with poor oral bioavailability seldom produce significant clinical levels in human milk, and are generally poorly absorbed by the infant as well.
- Drugs that transfer into the brain compartment also likely transfer into human milk, although this does not mean that levels in milk are clinically high or even clinically relevant.
- The transfer of drugs into human milk is one of the purest forms of compartment pharmacokinetics. A good knowledge of the kinetics and chemistry of a medication aids in predicting levels in human milk. However, nothing betters a well-conducted clinical trial in a human model.

INTRODUCTION

The rates of breastfeeding have continued to increase in the United States; according to the Centers for Disease Control and Prevention, approximately 76.5% of infants born in 2013 were breastfed and about 49% were continuing to breastfeed by 6 months of age, with approximately 16.4% of these infants still exclusively receiving breast milk at 6 months.[1] Although there are many social factors that lead to this high rate of discontinuation, the use of medications must be considered. The average number of different medications (excluding iron, minerals, folic acid, and vitamins) taken per mother in a small American study was 4 throughout lactation (0.9 medications per month).[2]

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With so many women using drug therapy during lactation, pediatricians and obstetricians are faced with the challenge of determining which medications are suitable for breastfeeding mothers. Although there is more literature available about the transfer of medications into breast milk, this is often not communicated to students and clinicians; therefore, many women are advised to stop breastfeeding or avoid drug therapy based on information obtained from product monographs.

Even without specific medication data from human studies, a good understanding of kinetic principles and mechanisms of medication entry into breast milk can help a clinician make an informed decision that often allows the mother to continue breastfeeding while treating her medical condition. This article discusses the most important concepts in understanding how medications enter breast milk so as to aid in clinical decision making, and highlights suitable medications for breastfeeding mothers.

KEY CONCEPTS OF MEDICATION ENTRY INTO BREAST MILK

Although all medications enter milk to some degree, clinically relevant levels are seldom attained. Most drugs simply transfer in and out of the milk compartment by passive diffusion from a region of high concentration to a region of low concentration. While some active transport systems exist for immunoglobulins, electrolytes, and particularly iodine, facilitated transport systems are rather limited. The authors know of fewer than 10 drugs that are selectively transported into human milk.

Medications that enter breast milk will often share certain physicochemical characteristics.[3] These agents are generally low in molecular weight (<500 Da), often attain higher maternal plasma levels, are generally poorly bound to plasma proteins, and have a higher pK_a (pH at which drug is equally ionic and nonionic; polar or ionic medications are less likely to leave the breast milk compartment). Human milk has a lower pH (7–7.2), which causes some medications with a higher pK_a (>7.2) to become ionized and trapped in milk.

In addition, clinicians also need to consider the oral bioavailability of the drug in the infant's gastrointestinal tract. Many drugs simply are not absorbed in the gastrointestinal tract of infants. The stage of lactation is important. Although more medication can enter breast milk in the colostral phase, only minimal doses are transferred to the infant during this phase, owing to the limited volume of colostrum. With mature milk there is a larger volume, but less medication enters breast milk because of tight cell-to-cell junctions.

CALCULATING INFANT EXPOSURE

Perhaps the most useful tool in clinical practice is to calculate the actual dose received by the infant. To do so, one must know the actual concentration of medication in the milk and the volume of milk transferred. Though not always available, data on milk levels for many drugs do exist.

More recent studies now calculate the average area under the curve (AUC) value for the medication (C_{ave}).[4] This methodology accurately estimates the average daily level of the drug in milk, and hence the average intake by the infant.

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 the 150 mL/kg/d value to estimate the amount of milk ingested by the infant. The