Lactation and drugs

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Abstract

Breast-feeding is the preferred form of infant nutrition. The vast majority of medications are safe for lactating mothers and their children, and insufficient information on drugs and lactation often leads to unwarranted premature weaning due to fear of potential risk to the child. Occasionally, lack of knowledge may also lead to drug-induced reduction of milk supply. Basic pharmacological knowledge will assist paediatricians in caring for nursing dyads. Important, interrelated concepts include the milk:plasma ratio and its variation over time, the relative infant dose, and differences in milk transfer and infant clearance of drugs with gestational and chronological age. In general, the safest drugs are those that are ionised, protein bound, of high molecular weight, lipid insoluble, and of normal to lower pH. Reference works are available to assist physicians in their assessment of the risks and benefits of specific drugs in individual patients.

Keywords lactation; breast-feeding; human milk; pharmacology; pharmaceutical preparations; pharmacokinetics

Introduction

Breast-feeding is the preferred form of infant nutrition. The World Health Organisation,[1] along with many other public health organisations, advises exclusive breast-feeding for the first 6 months, with the addition of culturally appropriate solid foods at that point, and continuation of breast-feeding through at least the second year of a child's life.

Since many drugs (e.g. ibuprofen) are 'off limits' for women during pregnancy, one of the first questions a new mother may ask after delivery is ''How can it be acceptable for me to take these pain medications while I am breast-feeding?'' In fact, the vast majority of medications are safe for lactating mothers and their children. Yet studies have shown that insufficient information on drugs and lactation often leads to unwarranted premature weaning, or non-compliance with a safe drug, due to fear of potential risk to the child.[2,3]

Because of the well-documented importance of human milk to child health, the risk of interruption or cessation of breast-feeding must be carefully weighed against the necessity and the risk of the medication under consideration. In some cases, a woman may be able to take a different medication, or forego pharmacotherapy together, rather than stop breast-feeding.

Unfortunately, new drugs are usually marketed without data regarding their use in pregnant women or nursing dyads. The US Centers for Disease Control recently issued a statement regarding the urgent need for a comprehensive, coordinated approach to gathering and disseminating such information.[4] Until such a unified source of data is available, paediatricians can use basic pharmacological principles and various published resources in caring for nursing infants and their mothers. This review will cover the principles relevant to use of these resources, and some examples of considerations applicable to the use of specific drugs in clinical practice.

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Pharmacokinetics and milk

When considering the relevance of pharmacokinetics to the breast-feeding dyad, we should start with what mothers and physicians want to know: how likely is it that a drug taken by the mother will affect her baby via her milk?

Routes of entry into milk

The baby's plasma concentration of the drug depends on the mother's plasma concentration, but also on several other factors. The function of the mammary alveolar cells is the synthesis of the components of milk (proteins and fat globules), and these cells do not 'excrete' drugs into milk in the same way that the kidneys excrete drugs into urine. Drugs may pass into the milk incidentally through one of two means.

Paracellular pathway: During the first 48–72 hours post-partum, the alveolar epithelium is still developing. At this time, there are still gaps between the cells that permit the entry of drugs from the interstitial fluid directly into milk to a greater extent than is possible later. This process of aqueous diffusion is called the paracellular pathway of drug transfer. Since the total volume of colostrum is small, the total amount of drug transferred is usually minimal despite the relatively higher concentration. However, because of this paracellular pathway, drug use in the early post-partum period should still be approached on a case-by-case basis.

Transcellular pathway: After the first few days post-partum, the intercellular gaps have closed and transfer of drugs into milk must occur via the alveolar epithelial cells themselves. This process usually involves passive diffusion across the lipid cell membrane, first into the cell from the capillaries and then out again into the milk. Some lipid-soluble drugs may dissolve into fat droplets synthesised by the cells, and are then co-secreted and thereby concentrated in the milk. Active transport has also been reported for a few other drugs, for which milk concentrations may greatly exceed maternal plasma concentrations. For example, iodides, especially radioactive types such as iodine-131, should be avoided as they may concentrate in milk due to the alveolar cell wall pump.

Plasma vs milk compartments

Because drugs must cross the alveolar epithelium before entering milk, the milk compartment is considered separately from the plasma compartment when evaluating a drug's lactational pharmacokinetics. Factors influencing entry into the milk compartment include:

- protein binding – the more protein bound the molecule, the less likely it is to enter the milk,
- lipid solubility – the more lipid soluble the molecule, the more likely it is to enter the milk,

- molecular weight – the larger the molecule, the less likely it is to enter the milk and
- pH – the more basic the molecule, the more likely it is to be 'ion trapped' in milk by the milk's slight relative acidity.

The milk:plasma ratio (*M/P*) is a concept that is useful in understanding the fact that these two compartments are separate in the mother. *M/P* ratios for individual drugs are often available to physicians in reference works. However, the *M/P* ratio alone is not sufficient for weighing the implications of a given maternal medication for the nursing child.

Drug bioavailability to infants

There are several reasons for this. Firstly, the concentration of drug in the milk (C_{milk}) is more relevant than the *M/P*. Secondly, in most cases both C_{milk} and *M/P* are constantly changing as the mother metabolises and clears the drug; thus, these concepts are better represented as areas under curves, rather than as set points or numbers in time. Thirdly, there are other factors that influence a drug's effect on a given infant; most notably, absorption from the stomach, in addition to distribution and clearance within the infant's body. For example, the acid environment of the stomach denatures many drugs. Also, many drugs undergo first-pass metabolism by the liver without ever reaching the infant's plasma compartment.

In short, the mere presence of a drug in milk does not necessarily mean that it poses any meaningful risk to the infant who will ingest that milk.

Estimating risk of exposure

Infant dose received via milk

The infant dose per kg per day may be estimated using the maximum or average milk concentration of the drug in question and a theoretical milk intake of 0.15 L/kg/day in an infant who is fully breast-fed. (Again, it should be noted that if a drug is not orally bioavailable, its milk concentration is virtually meaningless from a clinical viewpoint.)

Usual therapeutic infant dose

For drugs that are routinely prescribed to infants, the usual therapeutic infant dose may be used as a standard of comparison for the dose received in milk. If the dose an infant receives via milk is less than would be needed for clinical treatment, it is unlikely to represent a significant risk.

Relative infant dose

The 'relative infant dose' represents the ratio of the dose an infant would receive in milk to the usual adult dose. It is especially useful when considering the use of medications not usually given to infants. (However, the concept of relative infant dose is most useful in healthy term infants with 'normal' clearance of drugs and should not be a sole consideration in preterm or sick infants. These cases are addressed further below.)

To estimate the relative infant dose, the infant dose in mg/kg/day is divided by the therapeutic adult dose in mg/day per theoretical average adult weight (60 or 65 kg):

Relative infant dose (%) = Infant dose (mg/kg/day)/Maternal dose (mg/kg/day) × 100.

A safe relative infant dose is arbitrarily defined as no more than 10% of the adult dose, but because of the multiple factors involved in drug bioavailability, it is usually well below this threshold. This is true even for drugs in which milk concentrations greatly exceed maternal plasma concentrations.

Exposure index

The concept of 'exposure index' goes beyond that of 'relative infant dose' by incorporating the function of clearance with *M/P* ratio in a hyperbolic function:

$$\text{Exposure index } (\%) = A \times (M/P)/C\text{Li} \times 100,$$

where *A* is the average milk intake (e.g. 0.15 L/kg/day or 0.1 mL/kg/minute) and *C*Li is the infant clearance (mL/kg/minute).

An exposure index of less than 10% is generally accepted as safe.

The difference between relative infant dose and exposure index is that the exposure index takes the infant's clearance into

Resources on drugs and lactation

Print

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Table 1