

Neonatal drug exposure through breast milk

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Scope of the lecture:

In clinical settings, consultations on compatibility of maternal medications with breastfeeding are one of the most common requests. In this presentation, key principles and facts of drug safety in breastfeeding will be discussed, which are important for interpretation of drug levels in human milk.

Learning objectives:

1. Become aware of the medical benefits of breastfeeding
2. Recognize mechanisms of drug secretion into milk
3. Be able to articulate key factors for infant drug exposure through milk

Extended abstract:

Introduction

In our clinical service in Toronto, Canada, we receive nearly 25000 inquiries/year about drug safety in pregnancy and breastfeeding, and about 30% of these inquiries are about breastfeeding. Although safety information on medication use in breastfeeding is still limited, an advice to simply discontinue breastfeeding as often seen in drug labeling is not acceptable due to emerging evidence of medical benefits of human milk. Fortunately, drug monitoring in milk samples is feasible in both clinical and research settings. Based on pharmacokinetic principles, interpretation of such drug monitoring data for safety assessment is also possible.

Benefits of breastfeeding

Breastfeeding is essential for the mother and infant. It provides not only necessary nutrients to the infant, but also beneficial effects on infant development and maternal health, which range from infection prevention and enhanced cognitive function of the infant, and decreased risks of cancer in the mother's reproductive organs. Overall, reduction of infant infection is about 2-fold, and differences of IQ are about 7-8 points in favor of breastfed infants.¹⁻¹¹ Because of these benefits, professional organizations such as the American Academy of Pediatrics recommend exclusive breastfeeding for the first 6 months of life.² However, risk assessment is challenging if the mother requires medications.

Challenges in risk assessment

It is becoming increasingly common to see postpartum women on medications with an estimated prevalence of 66% or more, signifying the magnitude of the problem.^{12,13} We showed that many of these women are advised against breastfeeding, or to avoid taking necessary drugs, due to lack of rational risk assessment, resulting in discontinuation of breastfeeding in almost half of them.¹⁴⁻¹⁶ On the other hand, when drug therapy continues based on empirical evidence, cases of infants with serious drug toxicity emerge, including death.^{1,17-19}

Mechanisms of drug excretion into milk

Drugs administered to the mother enter the milk through various mechanisms. Diffusion and carrier-mediated transport, particularly through Breast Cancer Resistance Protein (BCRP), are the 2 main mechanisms, which are not mutually exclusive. BCRP (encoded by ABCG2)

belongs to a family of drug transporting proteins known as ATP-binding cassette (ABC) transporters. As a drug efflux pump, BCRP has a wide substrate spectrum including various anti-cancer drugs and toxins, expressed not only in drug resistant cancer cells, but also in tissues of barrier function such as intestinal epithelia and blood brain barrier. Importantly, BCRP (ABCG2) is highly induced in the mammary gland epithelial cells at a lactation stage due to prolactin-mediated activation of the JAK2-STAT5 pathway, compared to its non-lactating phase, while other ABC transporters such as P-glycoprotein (ABCB1) are down-regulated.^{20,21} This toxin pumping function of BCRP is apparently inconsistent with the role of the mammary gland in nurturing the infant, but it was later discovered that BCRP in the mammary gland is a vitamin B2 transporter.²²

Milk-to-(maternal) Plasma ratio of drug

In order to describe a magnitude of drug excretion into milk, a milk-to-(maternal) plasma ratio of drug AUCs (MP ratio) is frequently used. Because milk compartment is more acidic than maternal plasma, cationic compounds tend to be more ionized in milk than in plasma. As a result, they are trapped in the milk compartment due to inability of ions to diffuse back into maternal plasma across lipid bilayer. This phenomenon known as “ion trapping” causes accumulation of these drugs in milk with MP ratio ranging mostly from 1 to 5 for basic (cationic) drugs. Other factors, which influence MP ratio, include plasma protein binding and lipid solubility of drug. Although MP ratio greater than 1 indicates drug accumulation in milk, it is important to recognize that MP ratio by itself is not a determining factor for toxicity risk. MP ratio indicates neither a balance between mother’s and infant’s doses, nor a ratio of mother’s and infant’s plasma levels. It simply states a drug concentration in milk as a fraction of maternal plasma levels.

Relative Infant Dose

Average drug concentrations in milk may be translated into an infant daily dose of the drug through milk after multiplied by estimated milk intake of the infant (i.e., 150 ml/kg/day). This infant daily dose of the drug (per body weight: e.g., mg/kg/day) in milk can be compared to a therapeutic dose of an infant; if unavailable, a maternal dose per body weight may be used. This infant dose through milk expressed as % of an therapeutic dose is Relative Infant Dose (%). In theory, this is equivalent to Exposure Index (%): 100% is the same as a dose for therapy, and 10% is 1/10 of the therapeutic dose.¹ Assume below that two different drugs (A and B) are compared for their compatibility with breastfeeding:

Drug A has a maternal plasma level of 1 µg/ml and MP ratio of 5 (i.e., accumulated in milk): Because Drug A concentration in milk is $1 \mu\text{g/ml} \times 5 = 5 \mu\text{g/ml}$, the infant would receive 0.75 mg/kg/day of Drug A ($5 \mu\text{g/ml} \times 150 \text{ ml/kg/day} = 0.75 \text{ mg/kg/day}$). Assume that a therapeutic dose of Drug A for an adult is 75 mg/kg/day: Relative Infant Dose (RID) is 1%. The infant would ingest Drug A through milk at 1% dose of its therapeutic dose per body weight.

Drug B has an adult therapeutic dose of 0.3 mg/kg/day, an MP ratio of 0.1 (i.e., no accumulation) and a maternal plasma level of 10 µg/ml. An infant dose through milk is 0.15 mg/kg/day: ($10 \mu\text{g/ml} \times 0.1 \times 150 \text{ ml/kg/day}$). Because an adult therapeutic dose is 0.3 mg/kg/day, RID of Drug B is 50%, half of its therapeutic dose per body weight, which is substantially higher than Drug A above.

Clearly, when different drugs are compared, MP ratio may not provide decisive information for exposure level assessment. In most cases, RID is lower than 10%, and only handful of drugs achieve RID greater than 10% on average, although rarely exceeds 50%.

Infant Drug Clearance

An average concentration of the drug at steady state is proportional to Dose/time and bioavailability, and inversely proportional to Clearance of the drug. Overall, neonatal drug exposure through milk is characterized by a low dose and potentially reduced drug clearance, which is increasing due to on-going maturation process. Because each drug has a different combination of multiple elimination pathways, each of which follows different developmental trajectory, it is challenging to predict infant drug clearance of a particular drug. In this regard, physiologically-based pharmacokinetic (PBPK) modeling and simulation becomes a powerful tool.

Summary

Drug exposure through breast milk in the neonatal period poses a challenging problem. However, monitoring data of drug in milk can be used to estimate infant exposure levels. Coupled with knowledge on infant developmental process of drug elimination pathways, which is further supported by PBPK modeling and simulation, these drug monitoring data may be translated into infant plasma level prediction for rational risk assessment.

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