Pediatric Pharmacotherapy

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Maternal Medication Use During Breastfeeding

Pharmacology Literature Reviews

Assessing and Minimizing the Risk

Assessing the risk of maternal medication use in the breastfeeding infant continues to be one of the more difficult tasks faced by health care providers in obstetrics, pediatrics, and family medicine. Despite the dramatic increase in the percentage of women choosing to breastfeed, our knowledge of the safety of most medications remains limited. Research into the quantity of drug transferred into milk is complex and provides only a limited degree of certainty on the safety of medication use.[1,2] However, this lack of scientific data should not lead to the conclusion that most medications are unsafe. Case reports and surveillance studies frequently provide examples of maternal medication use that does not result in adverse effects for the breastfeeding infant.

While it is important not to underestimate risk to the infant, health care providers should avoid overemphasis of potential toxicity. In a study from the MotheRisk surveillance program in Canada, the authors found that 15% of mothers given prescriptions for antibiotics failed to initiate therapy, despite being given information on the safety of these medications.[3] Although it was not recommended to them, another 7% stopped breastfeeding during treatment. It

is evident that thorough counseling, throughout lactation, is needed to allay fears and avoid maternal noncompliance or unnecessary termination of breastfeeding.

Determining the Degree of Drug Transfer

Human milk is a suspension of protein and fat globules in a carbohydrate-based suspension.[1] The mechanisms by which medications are transferred into breastmilk are no different than those governing passage into any other maternal body fluid or organ system. Most drugs are transferred across membranes by passive diffusion, reaching a concentration equilibrium with the concentration in the blood. Other factors affecting the degree of transfer into a given fluid or tissue include the lipophilicity of the compound, the degree of ionization, and the extent of protein binding. Medications with a low molecular weight that are nonionized and lipophilic are the most likely to be transferred into breastmilk.

In addition to passive diffusion, medications also may be transferred into breastmilk incorporated within fat globules or bound to proteins, primarily casein and lactalbumin. Highly protein-bound drugs, though, are unlikely to cross extensively into breastmilk, since these drugs bind preferentially to serum albumin.[2,4]

There is no simple method for determining the amount of drug present in a given quantity of breastmilk. In addition to the physicochemical properties of the medication, maternal and infant factors must be considered. The composition of breastmilk changes greatly from the initial colostrum to mature milk. For example, lipophilic drugs such as diazepam are likely to be present in greater quantity in the milk of women who have been breastfeeding for several months than in the milk of women who have recently given birth. Protein concentration, however, is greater in colostrum than it is in mature milk.[2,5]

Even during a single breastfeeding session, milk composition will vary, with milk expressed towards the end of a feeding having a greater fat content. Blood flow to the breast as well as differences between milk and blood pH affect drug transfer and cause "trapping" of drugs that are weak bases within the milk already produced.[2] On the part of the infant, sucking patterns, duration of feeding, and volume consumed play a role in determining the amount of drug ingested. Once ingested, the drug must cross into the infant's bloodstream to exert systemic toxicity.

The medical literature in the field of drug transfer into breastmilk often refers to mathematical models to assess potential quantity consumed. The milk to plasma ratio (M/P) is equivalent to the drug concentration in the breastmilk divided by the maternal serum concentration. This value is an attempt to identify the equilibrium concentration between breastmilk and blood. The primary drawback of this method is that it relies on a one-point determination and does not reflect the other variables affecting drug transfer. In fact, the true M/P ratio can vary considerably during a single episode of breastfeeding.

Other studies refer to the percent of maternal dose ingested. This value is obtained by multiplying the drug concentration in the milk by the estimated milk

volume and dividing the result by the maternal drug dose. This number is then multiplied by 100 to give a percentage. While this method incorporates more of the variables involved, it still does not accurately assess the amount of drug which actually enters the infant's bloodstream. Neither method incorporates the effect of drug accumulation with repeated ingestion, nor do they account for the presence of any pharmacologically active metabolites.

Recently, a new model has been proposed which attempts to remedy these problems by combining M/P ratio with a pharmacokinetic estimate of drug clearance.[6] Although still limited in its predictive ability, it nevertheless offers a more accurate estimate than previous methods.

Another new approach to research in this area has been the assessment of multiple, matched serum and milk concentrations. For example, recent studies of gentamicin and terfenadine disposition in breastmilk have been published which include samples taken over 7 and 30 hours, respectively.[7,8] These multiple samples provide a better estimate of the variations in drug transfer during a period of several feeding sessions. Clinicians should be aware that, regardless of the model or method used, estimates of drug transfer should only be used to aid in the evaluation of risk, in conjunction with assessment of the infant's response.[2]

Minimizing Risk to the Infant

When a medication is being considered for use in a lactating mother, several questions should be addressed before initiating therapy. Is the drug necessary or could it be replaced with a nonpharmacologic or less toxic therapy? What information is available on the transfer of the drug into breastmilk and the pharmacokinetics of the drug in newborns? Is it a drug safely used to treat infants? If so, maternal use is unlikely to cause significant toxicity in the breastfeeding infant, since the concentration in milk will likely be much less than that achieved in the serum during therapeutic use. In cases where maternal treatment is unavoidable, the American Academy of Pediatrics has recommended the following steps to minimize risk to the infant.[9]

Table 1. Methods to Reduce Exposure

- - Select a drug that does not cross easily into breastmilk.
- - Select an agent with less risk of toxicity (e.g. acetaminophen instead of aspirin).
- - Use an alternative route of administration if possible (e.g. topical, inhaled).
- - Attempt to time breastfeedings to coincide with trough milk concentrations, usually by taking a dose just after breastfeeding or before the infant's longest sleep cycle.
- - Utilize serum and urine monitoring of drug concentrations if available.
- - If only short-term therapy of a potential toxin is required, consider temporary discontinuation of breastfeeding for four to five half-lives. Recommend a suitable replacement formula or use pre-expressed breastmilk.

- - If possible, delay treatment until weaning has occurred.

Toxicity in the infant is not the only potential adverse effect of maternal medication use. New research has revealed an effect on infant metabolism. Maternal use of medications which induce hepatic metabolism appears to stimulate the breastfeeding infant's liver as well as the mother's. In a similar manner, drugs which inhibit metabolism have been found to slow function in both mother and child.[10] We are only beginning to comprehend the complexity of the relationship between maternal medication use and long-term effects on the nursing infant.

While most medications are considered compatible with breastfeeding, there are substances (both medications and illicit drugs) for which the risk of toxicity is considered to be greater than any perceived benefit. The following table has been adapted from the current recommendations of the American Academy of Pediatrics.[9]

Table 2. Substances Contraindicated During

Breastfeeding

- amphetamine
- bromocriptine (decreases milk production)
- cocaine
- cyclophosphamide
- cyclosporine
- doxorubicin
- ergotamine
- heroin
- lithium
- marijuana
- methotrexate
- nicotine
- phencyclidine (PCP)
- phenindione

Mothers should be made aware of the potential for toxicity in their infants with these substances and, in those cases where therapy is unavoidable, should be advised to plan on using infant formula and/or discontinue breastfeeding.

Substances that should be used with caution in the breastfeeding mother include 5-aminosalicylic acid, antidepressants, antipsychotic medications, aspirin, benzodiazepines, chloramphenicol, clemastine, metoclopromide, phenobarbital, primidone, and sulfasalazine. This recommendation for caution is based on a limited number of case reports describing adverse effects.

Breastfeeding should be temporarily discontinued if maternal administration of metronidazole (single-dose therapy) or radiopharmaceuticals is required.

Metronidazole requires 12-24 hours for complete elimination. The time required for cessation after exposure to specific radioactive compounds has been established by the Committee on Drugs of the American Academy of Pediatrics.[9]
The counseling of breastfeeding mothers who require medical therapy is a complex issue. Unfortunately, simple yes or no answers are rarely adequate. It is up to the mother's and infant's health care providers to weigh benefit versus risk and attempt to minimize toxicity. For assistance, please contact the Children's Medical Center pharmacy at 982-0921 or the Drug Information Service at 924-8034. For assistance with breastfeeding management, please contact a UVA lactation consultant through the paging operator at 924-0000.
While it is reassuring that an increasing amount of data has become available on maternal medication use in recent years, there is still a need for further research in this area as well as case series and surveillance reports describing the outcomes of maternal treatment during lactation.

References

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Pharmacology Literature Review

Antibiotic Comparison

In this review, the authors compare and contrast five relatively new oral antibiotics: cefprozil, cefpodoxime, loracarbef, cefixime, and ceftibuten. The last of these agents has just recently been approved for use in the United States. The pharmacokinetic profiles, microbiologic activity, efficacy in clinical trials, adverse effects, and cost of these agents are evaluated. Both adult and pediatric data are included. Particular attention is given to the differences in gram positive coverage. The authors conclude that while these agents appear as effective as standard therapies and offer the advantage of less frequent dosing, their increased cost places them as second-line therapy behind traditional oral antibiotics. Schatz BS, Karavokiros KT, Taeubel MA et al. Comparison of cefprozil, cefpodoxime proxetil, loracarbef, cefixime, and ceftibuten. **Ann Pharmacother 1996;30:258-68.**

Cyclosporine-Drug Interactions

This article is an in-depth review of the drug interactions reported with cyclosporine to date. The material is divided into those interactions which have been well documented in the medical literature and those which have only been suggested in isolated case reports. The drugs are categorized by the nature of their interaction. An extensive section is devoted to the drugs which interfere with or induce cyclosporine metabolism. Campana C, Regazzi MB, Buggia I et al. Clinically significant drug interactions with cyclosporin(e): An update. **Clin Pharmacokinet 1996;30:141-79.**

Diagnosis and Treatment of Epilepsy

The authors of this review are known for their extensive publications in the field of epilepsy management. They present a concise review of seizure types, with a discussion of their treatment and prognosis. A comprehensive table of therapies for each seizure type is provided. In the second half of the article, the authors focus on newer antiepileptics, gabapentin, lamotrigine, vigabatrin, and felbamate. Morton LD, Pellock JM. Diagnosis and treatment of epilepsy in children and adolescents. **Drugs 1996;51:399-414.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 3/22/96:

- Anastrozole (Arimidex®) was added to the formulary. This agent is a nonsteroidal aromatase inhibitor used for treating advanced stages of breast cancer.
- Cisatracurium (Nimbex®), an intermediate-acting nondepolarizing neuromuscular blocking agent, replaces atracurium on the formulary. Like atracurium, cisatracurium

undergoes Hofmann degradation. Unlike atracurium, it does not produce an increase in serum histamine. It is more potent, resulting in potentially less production of laudanosine, a metabolic byproduct which has been associated with seizures in animals. Cisatracurium is approximately half the cost of atracurium in equipotent doses. In children ages 2-12 years, the dosage is 0.1 mg/kg for a single injection. For continuous infusion, an initial dose of 3 mcg/kg/min is recommended, followed by a maintenance infusion of 1-2 mcg/kg/min, titrated to the desired depth of paralysis.

- A therapeutic substitution protocol for H_2-antagonists was adopted. The policy was developed because of the therapeutic similarities of these agents and the differences in purchasing costs. Nizatidine (Axid®) is now the **oral** H_2-antagonist of choice. Famotidine (Pepcid®) is the **intravenous** agent of choice. Ranitidine use will be restricted to pediatrics, since nizatidine is not available in an oral liquid formulation. Cimetidine was removed from the formulary, primarily due to lack of use.

If you have comments, questions, suggestions, or would like
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