CHRONIC ILLNESS AND THE BREASTFEEDING MOTHER

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ABSTRACT

Medications taken for chronic illness (e.g., depression, epilepsy, immunological conditions) while breastfeeding pose challenges to risk-assessment. Based on several cases of drug toxicity (or lack thereof) in the breastfeeding infant, individual risk:benefit analyses are discussed. The benefits of human milk are highlighted, together with clinically important principles for patient management, the spectrum of adverse effects in the infant, and emerging concerns regarding the safety of some medications during breastfeeding. A practical guide for patient management is presented.

Key Words: *Breastfeeding, breast milk, chronic disease, antidepressants, antiepileptics, anxiolytics, antipsychotics, information sources*

INTRODUCTION

It is well known that breastfeeding is a healthy, simple and inexpensive way to nourish an infant. The benefits of breastfeeding include protection of the child against common childhood illnesses and improved cognitive function; for the mother, there is a lower risk of breast and ovarian cancer.[1] Breastfeeding incidence has increased since the 1970s, with more women breastfeeding longer in both Canada and the U.S.[2-5]

Where a mother is being treated for a chronic illness, a number of questions arise regarding breastfeeding. These will be addressed.

- How much drug is in breast milk?
- What kinds of drugs are highly excreted in milk? What about antidepressants, antiepileptics, anxiolytics, antipsychotics?
- Can mothers breastfeed while on drugs?
- Is there a clinically useful resource on this topic?

How much drug is in breast milk?

Drugs get into breast milk by crossing epithelial barriers from the maternal plasma. Carrier-mediated transport, together with diffusion based on the physicochemical properties of each drug, may modulate drug transfer from maternal plasma[6] (pH 7.4) to milk (pH 7.0). The milk-to-plasma (M/P) ratio is the comparison of drug concentrations between the two compartments, which can be used to determine the amount of drug delivered to the infant. The calculated amount, using an average milk intake of 150 ml/kg/day, can then be compared to therapeutic doses to identify whether this is problematic or not. Mere presence of drug in the mother's milk is not a contraindication to breastfeeding; other factors must also be considered, e.g., infant capacity to eliminate the drug, drugs with dose-independent effects, underlying morbidity, concurrent treatments.

Example

The M/P ratio of Drug A is 2. A breastfeeding mother takes 10 mg every 4 hours: 60 mg per day or approximately 1 mg/kg/day. Let's assume that her average drug plasma level is 0.1 mcg/mL. The average breast milk level is 0. 2 mcg/mL (0.1 x MP ratio of 2 = 0.2).

Her infant feeds at a rate of 150 mL/kg/day of breast milk and so receives 30 mcg/kg/day (0.03 mg/kg/day) of Drug A from the mother.

Even if Drug A is concentrated in milk (i.e., MP ratio of 2), the dose the infant receives is about 3% of the mother's dose on a weight basis, which is probably too low to cause any recognizable effects. This is why a focus on MP ratio alone is not useful in actual risk assessment.

Of note is that fetal drug exposure during pregnancy is usually much higher than after birth through breastfeeding, when infants are no longer exposed to the same high plasma levels and begin clearing the drug themselves.

What kinds of drugs are highly excreted in milk? How much of an antidepressant is excreted in milk?

In 2004 we published the findings of a literature search for studies on select central nervous system drugs, their levels in breast milk, and infant exposure as a result of breastfeeding.[7] The case numbers were small, but we found that antidepressant exposure through breast milk is relatively small.[8,9]

Overall, the breastfed infant's exposure to selective serotonin re-uptake inhibitors (SSRIs – citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), to tricyclics (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline), and to other antidepressants (bupropion, lithium, befazodone, venlafaxine) as a percentage of the mother's dose per kilogram was in the range of 1% to less than 10% of the maternal dose. For some drugs, exposure to active metabolites was included in the calculation.

One case of lithium toxicity was reported, but this was confounded by the infant having been exposed to the drug in utero.[10] At Motherisk, we monitor lithium levels in breast milk due to the variability in concentration among women.[11]

How much of an antipsychotic is in milk?

The same analysis was done for antipsychotics (chlorpromazine, chlorprothixene, haloperidol, perphenazine, clozapine, olanzapine, risperidone).[7] Again the findings showed that exposure of the infant to these drugs through breast milk was probably small, i.e., from under 1% to less than 10% of the mother's dose per kilogram.

We investigated one case of quetiapine in breast milk, measuring levels that were much less than 1% of the mother's weight-adjusted dose.[12] The mother had been taking the drug throughout her pregnancy and wished to continue her treatment post-partum while breastfeeding her newborn. After the results came back, she initiated breastfeeding at week 8 and follow-up at 4.5 months showed no adverse effects noted on the infant, who was developing well.

How much of an anxiolytic is in milk?

The published findings for anxiolytics (clonazepam, diazepam, oxazepam, lorazepam, temazepam) again showed that infant exposure would be expected to be low, although there were differences among the agents.[7] Diazepam levels showed a broader range than the other drugs, extending from below 1% to less than 20% of the mother's dose per kilogram.

How much of an antiepileptic is in milk?

Antiepileptics (carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone, valproic acid, gabapentin, lamotrigine, topiramate, vigabatrin) had a wide range of findings among the different drugs, and some showed high exposure of the breastfeeding infant.[7] Ethosuximide, phenobarbital and primidone reached levels over 50% of the mother's dose per kilogram. Although this exposure may not mean an adverse result for the infant, agents affording lower exposure levels are available.

Adherence to Drug Therapy or to Breastfeeding

Public literature, advice from various sources, and mothers' worries about harming their babies through breastfeeding continue to influence adherence to drug therapy in new mothers. Even antibiotic compliance has been shown to be affected, with some mothers never starting acute treatment and others discontinuing breastfeeding while on antibiotics.[13]

Mothers on antiepileptic therapy have shown a trend towards choosing formula feeding over breastfeeding.[14] As discussed above, there are antiepileptic drugs which the mother can take that will provide only minimal amounts to the breastfeeding infant.

Propylthiouracil is another long-term therapy that has been shown to deter mothers from breastfeeding.[15] In the study by Lee and colleagues, it was shown that physicians' advice significantly affected the choice to breastfeed, both for and against. Their results from a physician survey found that 44% of endocrinologists did not recommend breastfeeding

while a woman was on propythiouracil. We can therefore appreciate that it is not only popular news articles and friends' advice that can deter women from breastfeeding while on chronic drug therapy. Medical practitioners also affect patient behaviour and require education about the safety for infants of many chronic drug therapies in the breastfeeding mother.

INFORMATION SOURCES

One useful and readily accessible source of information for the practitioner is the web site LactMed from the U.S. National Library of Medicine (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT).

As the introduction to the site states, it is "Geared to the healthcare practitioner and nursing mother" and "includes information such as maternal levels in breast milk, infant levels in blood, potential effects in breastfeeding infants and on lactation itself, the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding, and alternate drugs to consider."[16] It can provide a one-stop source of information.

Research on drug levels in breast milk and safety in the nursing infant is required in order to fill in many information gaps. Recognizing that there are few data on drug levels in breast milk, i.e., excretion into breast milk of drugs taken by the mother, Dr. David Colantonio of The Hospital for Sick Children/Research Institute are investigating drug safety in lactation.[17] The study, conducted in collaboration with the Motherisk program, aims to identify which drugs or drug classes are excreted into breast milk and then to identify the risks to breastfeeding infants.[18] Priority drugs have been identified to be bupropion, citalopram, excitalopram, lithium, methotrexate, and venlafaxine.

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REFERENCES

1. World Health Organization: 10 facts on breastfeeding [Internet]. Geneva: World Health Organization; 2014 [cited 2014 Jun 29]; [11 screens]. Available from: http://www.who.int/features/factfiles/breastfeeding/facts/en/index2.html
2. Tanaka PA, Yeung DL, Anderson GH. Infant feeding practices: 1984-85 versus 1977-78. CMAJ 1987[cited 2014 Jun 29];136(9):940-944. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/3567809
3. Centers for Disease Control. Breastfeeding Report Card – United States, 2009 [cited 2014 Jun 29]. Available from: http://www.cdc.gov/breastfeeding/data/reportcard/reportcard2009.htm
4. Centers for Disease Control. Breastfeeding Report Card – United States, 2013 [cited 2014 Jun 29]. Available from: http://www.cdc.gov/breastfeeding/pdf/2013breastfeedingreportcard.pdf
5. Statistics Canada. Health at a Glance. Breastfeeding trends in Canada [Internet]. Ottawa: Statistics Canada; 2013-11-15 [cited 2014 Jun 29]. Available from: http://www.statcan.gc.ca/pub/82-624-x/2013001/article/11879-eng.htm
6. Koshimichi H, Ito K, Hisaka A, et al. Analysis and prediction of drug transfer into human milk taking into consideration secretion and reuptake clearances across the mammary epithelia. Drug Metab Dispos 2011[cited 2014 Jun 29];39(12)"2370-2380. Available from: http://dmd.aspetjournals.org/content/39/12/2370.full.pdf+html
7. Rubin ET, Lee A, Ito S. When breastfeeding mothers need CNS-acting drugs. Can J Clin Pharmacol 2004;11(2):e257-e266.
8. Weissman Am, Levy BT, Hartz AJ, et al. Pooled analysis of antidepressant levels in lactating mothers, breast milk, and nursing infants. Am J Psychiatry 2004[cited 2014 Jun 29];161(9):1066-1078. Available from: http://ajp.psychiatryonline.org/article.aspx?articleID=176862
9. Berle JØ, Spigset O. Antidepressant use during breastfeeding. Curr Womens health Rev. 2011[cited 2014 Jun 29];7(1):28-34. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3267169
10. Weinstein MR, Goldfield M. Lithium carbonate treatment during pregnancy; report of a case. Dis Nerv Syst 1969;30(12):828-832.

11. Moretti ME, Koren G, Verjee Z, Ito S. Monitoring lithium in breast milk: an individualized approach for breastfeeding mothers. Ther Drug Monit 2003;25(3):364-366.
12. Lee A, Giesbrecht E, Dunn E, Ito S. Excretion of quetiapine in breast milk. Am J Psychiatry [letter]. 2004 [cited 2014 Jul 5];161(9):1715-1716. Available from: http://ajp.psychiatryonline.org/data/Journals/AJP/3764/1715-a.pdf
13. Ito S, Koren G, Einarson TR. Maternal noncompliance with antibiotics during breastfeeding. Ann Pharmacother 1993;27(1):40-42.
14. Ito S, Moretti M, Lian M, et al. Initiation and duration of breast-feeding in women receiving antiepileptics. Am J Obstet Gynecol 1995;172(3):881-886.
15. Lee A, Moretti ME, Collantes A, et al.of breastfeeding and physicians' advice: A cohort study of women receiving propylthiouracil. Pediatrics 2000;106(1):27-30.
16. LactMed [Internet]. Bethesda (MD): National Library of Medicine (US), TOXNET Toxicology Data Network; 2013 Aug 5 [cited 2014 Jul 8]. Available from: http://www.nlm.nih.gov/news/lactmed_announce_06.html
17. Ito S, Colantonio D. "Drugs in Lactation" Analysis Consortium Phase 1. DLAC Phase 1. Catalyst Grant: Post Market Drug Safety and Effectiveness [Internet]. Ottawa (ON): Canadian Institutes of Health Research, Project Information; 2012 Feb 27 [cited 2014 Jul 8]. Available from: http://webapps.cihr-irsc.gc.ca/cfdd/db_search?p_language=E
18. Colantonio D. Laboratory Medicine and Pathology [Internet]. Toronto (ON): University of Toronto [cited 2014 Jul 8]. Available from: http://www.lmp.utoronto.ca/research/faculty-research-database/colantonio-david