Drug Excretion into Breast Milk: are all drugs contraindicated for breastfeeding?

David A. Colantonio[1], **Joshua Sha Ye[2]**, Sarah R. Delaney[3], Ellie Majdi[2], Shinya Ito[3]

[1]Department of Pediatric Laboratory Medicine, Hospital for Sick Children, 555 University Ave, Toronto, ON, Canada M5G 1Z8

[2]IONICS Mass Spectrometry, 32 Nixon Rd, Bolton, ON, Canada L7E 1W2

[3]Department of Pharmacology and Toxicology, University of Toronto, 1 King's College Circle, Toronto, ON, Canada M5S 1A8

INTRODUCTION: Current epidemiological research provides strong evidence for the health benefits associated with breastfeeding, including reduction in infant mortality, infection and development of chronic diseases, as well as a positive impact on cognitive development[1-5]. Current Centre for Disease Control Breastfeeding Report Card demonstrates more women (~ 80%) are breastfeeding and for longer[6]. However, studies have also shown that 66 - 80% of women are on medication during the postpartum period [7-9]. Consequently, this leads to an increased likelihood of infant drug exposure through breast milk. Although the dose of drug is considered to be small, there have been reports of adverse events and even fatality in infants exposed to drugs in breast milk [10-14]. Although not all drugs may be considered contraindicated while breastfeeding, there remains little data on this topic.

Methotrexate (MTX) is the first line of treatment for rheumatoid arthritis (RA), which has a high incidence in women of childbearing age. Disease activity of RA often decreases during pregnancy but tends to flare following delivery, necessitating the reestablishment of treatment. Only one case report on the excretion of MTX into breast milk has been published. Due to the paucity of data on MTX levels in breast milk, the potential risk of toxicity and drug accumulation in the infant remains largely unknown. We developed a sensitive and specific LC-MS/MS method to quantitate MTX and its metabolite in human milk and applied it to patient samples. We also calculated the relative infant dose of MTX to determine the risk to the infant. The objective of this study is to investigate the risk of drug exposure in nursing infants by determining drug concentrations in breast milk, with an aim to developing pharmacokinetic profiles for drugs excreted into breast milk.

METHODS: To investigate infant drug exposure through breast milk, we established a drug safety monitoring program, Drugs in Lactation Analysis Consortium (DLAC), to measure

several drugs commonly used by women breastfeeding, beginning with methotrexate. Breast milk is a complex lipid- and protein- rich matrix, with drugs partitioning to either the aqueous or lipid phase, thus requiring meticulous sample processing before analysis. Differences in the lipid and protein composition of milk exsists between fore and hind milk. We first investigated whether drugs partition to the aqueous or lipid phase of breast milk. We then worked to create a simplified drug extraction method using hexane, methanol and acetonitrile to facilitate efficient drug extraction from breast milk. Extraction efficiency and stability were determined.

Next, an LC-MS/MS method was developed to measure Methotrexate and its active metabolite, 7-hydroxymethotrexate. Briefly, methotrexate was measured using an IONICS 3Q 210 mass spectrometer. Detection was performed by multiple reaction monitoring (MRM) mode using electrospray ionization in the positive ion mode. Settings were as follows: ESI Voltage (Volts), 5000; Nebulizer Gas Setting, 400; Drying Gas Setting, 120; Heating Gas Setting, 350; Source Temp (^{0}C), 250; MTX MRM 455.1/308.0 and 455.1/134.0. Liquid chromatrographic separation was performed on a Shimadzu Prominence UFLC system, including binary pumps, autosampler, degasser and column oven. A sample volume of 5 µL was injected into an Imtakt C8 column (2.0 x 75 mm, 3 µm) at room temperature. The method was then validated according to standard clinical laboratory protocols. Briefly, the method was fully validated in terms of selectivity, linearity, accuracy, precision, stability and recovery. Comparison using patient samples was also performed.

Patients receiving MTX therapy for RA were recruited through the SickKids Motherisk Program for the DLAC Project or through the Rheumatology Clinic at Southlake Regional Health Centre in Newmarket, Canada. Whole breast milk samples were aliquotted and stored at -20°C until sample preparation, extraction and analysis.

RESULTS: Results from the method validation will be presented. Pharmacokinetic profiling of methotrexate and its metabolite in breast milk were determined following a subcutaneous dose of 25 mg/mL of methotrexate, once weekly. Breast milk samples were obtained at the following 7 timepoints: pre-dose (time zero), 1 hr, 12 hrs, 24 hrs, 48 hrs, 72 hrs and 96 hrs post-dose. Both

foremilk and hindmilk were measured. We found that MTX is excreted into breast milk, but with no notable differences in drug concentrations between foremilk and hindmilk. The highest drug concentrations occurred between 1-12 hours post-dose; the concentration steadily decreased between 12 – 48 hours, with small but detectable levels from 48 - 96 hrs.

CONCLUSION: Methotrexate is excreted into breast milk at significant concentration within the first 24 hrs post-dose. However, no notable differences in drug concentrations between foremilk and hindmilk were observed. Due to the difficulty in obtaining foremilk and hindmilk, this is the first study to measure and compare drug levels in this sample type. This data provides the foundation to establish a TDM system for measuring drug concentrations in breast milk, with the aim to carry out population-based pharmacokinetic analysis to determine safety guidelines on drug excretion into breast milk as well as breast feeding guidelines.

References

1. Section on breastfeeding, American Academy of Pediatrics: Policy Statement. Breastfeeding and the use of human milk. Pediatrics 2012; 129: e827-841.

2. Cunningham AS, Jelliffe DB, Jelliffe EFP, Breast-feeding and health in the 1980s: A global epidemiological review. J Pediatrics 1991; 118: 659-66.

3. Ruiz-Palacios GM, Calva JJ, Pickering LK, Lopez-Vidal Y, Volkow P, Pezzarossi H, West MS. Protection of breast-fed infants against Campylobacter diarrhea by antibodies in human milk. J Pediatr 1990; 11: 707-13

4. Mayer EJ, Hamman RF, Gay EC, Lezotte DC, Savitz DA, Klingensmith GJ. Reduced risk of IDDM among breasfed children. The Colorado IDDM Registry. Diabetes 1988; 37: 1625-32.

5. Kramer MS, Aboud F, Mironova E, Valinovich I, Platt RW, Matush L, Igumnov S, Fombonne E, Bogandovich N, Ducruet T, Collet JP, Chalmers B, Hodnett E, Davidovsky S, Skugarevsky O, Trofimovich O, Kozlova L, Shapiro S: For the Promotion of Breastfeeding Intervention Trial (PROBIT) Study Group. Breastfeeding and child cognitive development: New evidence from a large randomized trial. Arch Gen Psy 2008; 65: 578-584.

6. Centre for Disease Control Breastfeeding Report Card USA 2014. http://www.cdc.gov/breastfeeding/pdf/2014breastfeedingreportcard.pdf

7. Matheson I. Drugs taken by mothers in the puerperium. Br Med J 1985;290:1588-1599.

8. Schirm E, Schwagermann MP, Tobi H, de Jong van den Berg LTW. Drug use during breastfeeding. A survey from the Netherlands. Eur J Clin Nutr 2004; 58: 386-390.

9. Stults EE, Stokes JL, Schaffer ML, Paul IM, Berlin CM. Extent of medication use in breastfeeding women. Breastfeed Med 2007;2: 145-151.

10. Ito S. Drug therapy for breastfeeding women. N Eng J Med. 2000; 343: 118-126.

11. Ito S, Lee A. Drug excretion into breast milk: Overview. Adv Drug Deliv Rev 2003; 55:617-27.

12. Neuman G, Colantonio D, Delaney S, Szynkaruk M, Ito S. (2014). Bupropion and Escitalopram During Lactation. Ann Pharmacother 48(7): 928-931.

13. Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder SJ. Pharmacogenetics of morphine poisoning in a neonate of a codeine- prescribed mother. Lancet 2006; 368(9536):704.

14. Madadi P, Ross CJD, Hayden MR, Carleton BC, Gaedigk A, Leeder SJ, Koren G. Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: A case-control study. Clin Pharmacol Ther 2009; 85:31-35.