A Consensus Statement on the Use of Domperidone To Support Lactation

May 11th, 2012

Authors: Daniel Flanders, Aviva Lowe, Michael Kramer, Orlando da Silva, Carole Dobrich, Marsha Campbell-Yeo, Edith Kernerman, Jack Newman

Endorsed By

Dr. Yoel Abels, MD MHSc CCFP FCFP. Department of Family and Community Medicine, University of Toronto. Medical Director, Forest Hill Family Health Centre. Toronto, ON.

Dr. Elizabeth Asztalos, MD MSc FRCPC. Director, Neonatal Follow-up Programme, Division of Neonatology, University of Toronto. Director, The Centre for Mother, Infant, and Child Research, Sunnybrook Research Institute, Sunnybrook Health Sciences Centre. EMPOWER investigator. Toronto, ON.

Marsha Campbell Yeo, PhD NNP-BC. Maternal and Newborn Program , IWK Health Centre. EMPOWER investigator. Halifax, NS.

Lenore Goldfarb, PhD CCC IBCLC. Herzl Family Practice Centre - Goldfarb Breastfeeding Clinic, Jewish General Hospital. Montreal, PQ.

Dr. Michael Kramer, MD. Professor, Departments of Pediatrics, and of Epidemiology, Biostatistics and Occupational Health. McGill University, Faculty of Medicine, Montreal, PQ.

Dr. Orlando da Silva, MD MSc FRCPC. Associate Professor, Department of Paediatrics, Division of Neonatal-Perinatal Medicine. Children's Hospital, London Health Sciences Centre. London, ON.

Dr. Hilary de Veber, MD FRCPC. Newman Breastfeeding Clinic, Toronto, ON.

Carole Dobrich, RN IBCLC. Herzl Family Practice Centre - Goldfarb Breastfeeding Clinic, Jewish General Hospital. Montreal, PQ.

Dr. Daniel Flanders, MD FRCPC. Lecturer, Department of Pediatrics, University of Toronto, Faculty of Medicine. Newman Breastfeeding Clinic. Toronto, ON.

Edith Kernerman, IBCLC. Co-Director, Newman Breastfeeding Clinic. Toronto, ON.

Lynda Kirby, IBCLC. Better Breastfeeding Clinic, Toronto, ON.

Dr Cathryn Kuzyk, MD. Foothills Breastfeeding Clinic, Calgary, AB.

Dr. Aviva Lowe, MD FRCPC. Newman Breastfeeding Clinic. Toronto, ON.

Dr. Howard Mitnick, MDCM. Faculty Lecturer, Department of Family Medicine, McGill University. Herzl Family Practice Centre - Goldfarb Breastfeeding Clinic, Jewish General Hospital. Montreal, PQ.

Dr. Jack Newman, MD FRCPC. Assistant Professor, Department of Pediatrics, Faculty of Medicine, University of Toronto. Co-Director, Newman Breastfeeding Clinic. Toronto, ON.

Dr Graham Pratt, MD. Herzl Family Practice Centre - Goldfarb Breastfeeding Clinic, Jewish General Hospital. Montreal, PQ.

Dr. Leah Roth, MD FRCPC. Better Breastfeeding Clinic. Toronto, ON.

Dr Mary-Jo Woolgar, MD. Foothills Breastfeeding Clinic. Calgary, AB.

Dr Anjana Srinivasan, MDCM CCFP IBCLC. Faculty Lecturer, Department of Family Medicine, McGill University. Medical Co-Director, Goldfarb Breastfeeding Clinic - Herzl Family Practice Centre, Jewish General Hospital. Montreal, PQ.

Dr Meira Stern, MD. Medical Co-Director, Goldfarb Breastfeeding Clinic - Herzl Family Practice Centre, Jewish General Hospital. Montreal, PQ.

Dr. Eitan Weinberg, MD FRCPC. Newman Breastfeeding Clinic. Toronto, ON.

Dr. Jean Zigby, MD. Herzl Family Practice Centre - Goldfarb Breastfeeding Clinic, Jewish General Hospital. Montreal, PQ.

Introduction

Domperidone is a peripheral dopamine antagonist classically used to treat gastro-esophageal reflux and upper gastro-intestinal motility disorders. It is also used to prevent side effects associated with the treatment of Parkinson's Disease. It has been used in Canada since the mid-1980s, both in children and adults.

Domperidone also increases prolactin levels in the blood and has been used with success to increase milk supply in women with insufficient milk production[1]. It does this by blocking the D2 and D3 dopamine receptors in the pituitary gland. As a result, prolactin, the secretion of which is blocked by dopamine, now is liberated from the anterior pituitary and stimulates the milk producing cells of the breast.

It is thought that, under certain conditions, domperidone may increase the QT interval on ECG, thereby increasing the risk of Torsade de Pointes or other life-threatening arrhythmias[2]. In fact, there are many prescribed drugs which may increase the QT interval without seemingly increasing the risk of life-threatening arrhythmias. These include salbutamol, amitriptyline (and other tricyclic antidepressants), ciprofloxacin (and other fluoroquinolones), citalopram (and other SSRI's), clarithromycin (and other macrolides), diphenhydramine, and many other commonly used medications approved in Canada[3].

Currently, little is known regarding specific contraindications for domperidone when used as a galactogogue. However, until further studies are conducted, it is recommended not to prescribe domperidone to any mother with a history of known or suspected cardiac arrhythmias (tachyarrhythmia, QT prolongation); currently on an anti-arrhythmic medication; or having a chronic/debilitating illness, abnormal liver function,or serious gastric abnormality[4]. Caution should also be used in mothers concomitantly taking medications known to alter the metabolism of domperidone (via inhibiting the cytochrome P450 pathway), medications that have dopaminergic or antidopaminergic activity, and medications which may increase the QT interval[5].

Domperidone has previously been implicated as causal in arrhythmias when given intravenously in doses higher than would ever be used orally[6]. A warning advising against the use of domperidone by the Federal Drug Administration in the United States was published in 2004 based on the concern raised by high-dose intravenous administration of domperidone[7]. Of note, among the patients referenced in this warning, the majority had co-morbid serious illnesses, were receiving chemotherapy, and/or were severely hypokalemic[8]. Nonetheless, despite compelling arguments in opposition[8], domperidone was consequently withdrawn from the U.S. market. In September, 2011, The FDA granted orphan drug status to domperidone for "treatment of hypoprolactinemia in breastfeeding mothers". This may represent the first step towards domperidone returning to the US market as an FDA-approved medication specifically for lactation support.

Most studies on adverse effects of domperidone have looked at doses of 30 to 60 mg/day. These studies describe the following most commonly reported adverse effects: dry mouth, transient skin rash or itching, headache, thirst, abdominal cramps, diarrhea, drowsiness, and nervousness[9].

In March 2012, Health Canada endorsed an advisory statement, published by Teva Canada Limited, indicating that health practitioners should exercise caution when prescribing domperidone at doses greater than 30 mg/day[10]. The advice is based on the theoretical risk that higher oral doses of domperidone can trigger ventricular arrhythmias and sudden cardiac death. As detailed in the Critique section below, the justification for this advisory, especially in young breastfeeding women, is not supported by the scientific literature. Of primary concern is the likelihood that, based on the warning, many health practitioners will discontinue prescribing domperidone to mothers who would otherwise require it to support and sustain breastfeeding. As a consequence, numerous babies who would have otherwise breastfed will not. The adverse consequence of not breastfeeding along with the resultant introduction of artificial nutrition in infancy, carry serious associated morbidity and mortality for which there is scientifically solid, prolific, and compelling evidence[11-34].

Most studies on domperidone for lactation use a starting dose of 30 mg/day. No studies to date have looked at safety and efficacy of dosage titration up to a maximum dose. Amongst lactation specialists in Canada, domperidone is being prescribed in doses ranging from a starting dose of 30-90 mg/day to a maximum dose of

80-160 mg/day. Of the thousands of mothers the authors of this statement have collectively treated with domperidone for the purposes of breastfeeding support, no one is aware of a single case of maternal death from ventricular arrhythmia. In fact, Health Canada's Canada Vigilance Program has confirmed that between 1965 and 2011, there were no cardiac-related deaths reported among women taking Domperidone[35].

Critique

The recent Health Canada-endorsed warning published in March 2012[10] about the use of domperidone was based on data derived from two public health databases: one in the Netherlands[36] and one in Saskatchewan[37]. The warning was based on information gathered from an entirely different population than those who would be taking domperidone for breastfeeding purposes and is thus not generalizable to the lactating population. The average age of the patients in the studies was 72.5 years in one[36] and 79.4 years in the other[37]. Many of the patients in the studies had pre-existing health problems such as high blood pressure, coronary artery disease, and congestive heart failure.

There were, however, some notable trends that, when extrapolated to the breastfeeding population largely comprised of younger healthier women, are quite reassuring. In one study[37], the authors concluded that the risk of a cardiac problem related to taking domperidone in younger patients was much lower than in older patients. In fact, the risk quoted in younger patients was almost the same as that outcome occurring by chance alone (OR of 1.1 in those younger than age 60 compared with an OR of 1.64 in those older than age 60). That study also specifies that the risk in females was significantly lower than in males (OR of 1.25 in females compared with an OR of 2.23 in males).

The warning regarding the use of domperidone in higher doses (>30mg per day) was based on only one of the two studies[36]; the other study[15] did not include any information about dosing. In the one study where dosing information was included, out of the 1304 deaths that were studied, only 10 patients were taking domperidone at the time of death. Of those 10 taking domperidone, only 4 patients were documented to be taking higher doses of domperidone (>30mg per day). Thus, this Health Canada-endorsed dose-related warning comes from dosing data compiled from a total of four patients. In fact, the authors were not specifically cautioning physicians not to prescribe higher doses, but rather were suggesting that "it is important to avoid prescribing domperidone to patients with a high risk of sudden cardiac death". It is very hard to make a case for a drastic reduction in domperidone dosing in lactating women (wherein a dose of <30mg may not be sufficient to support lactation in a significant number of cases) when the data relied upon to generate the dosing warning was based on such a small number of cases that do not demographically resemble the population in which it is being prescribed.

Domperidone is generally used to treat gastro-intestinal problems, such as acid reflux. Some of the symptoms of heart disease may mimic symptoms of a gastro-intestinal illness. It is possible that some patients were taking domperidone for what was thought to be a gastro-intestinal problem when, in fact, the symptoms may have been related to a heart problem. While the authors attempted to account for this possible protopathic bias[36], it is hard to tease out the etiology of the potentially overlapping symptomatology. Furthermore, because domperidone is available over-the-counter in parts of Europe, it is conceivable that the number of people self-medicating with domperidone is higher than the rate actually quoted in the Dutch study (as the study only took into account prescriptions for domperidone[31] and not over-the-counter use). This important fact may have skewed the results. Some other important limitations of the studies include the fact that key pieces of information are unavailable including smoking status and use of other non-prescription drugs—both of which can be important factors[37] in affecting the study results.

In summary, breastfeeding mothers using domperidone do not fall into the same demographics as the patients involved in the studies from which the warning was generated. Furthermore, with caution about the use of higher doses of domperidone stemming from a study where so few patients were actually on those higher doses, the Health Canada-endorsed warning regarding the use of domperidone in higher doses seems to be an over-reaction. Finally, taking into account the other drawbacks of these studies as outlined above, the evidence that domperidone actually causes ventricular arrhythmias or sudden cardiac death is not compelling.

Future Research

A number of research initiatives are currently underway in Canada looking at the safety and efficacy of Domperidone when prescribed specifically as a galactogogue.

In Montreal, the Herzl Family Practice Centre - Goldfarb Breastfeeding Clinic has initiated a retrospective chart review of 400 registered patients who were prescribed domperidone at doses ranging from 80 to 120 mg/day. The review will focus specifically on the incidence and severity of side-effects and adverse events presumed to be secondary to taking domperidone, although the sample size will be insufficient to detect an increased risk of torsade de pointes or other ventricular arrhythmias.

This year, EMPOWER (a prospective, randomized, double-blinded, placebo-controlled trial) gets underway. This study will look specifically at the efficacy and safety of domperidone (30 mg/day) prescribed specifically for lactation support in 560 mothers of preterm babies in the Neonatal Intensive Care Unit setting. Over the course of the study, any adverse drug reactions will be reported directly to Health Canada. Furthermore, pre- and post-treatment maternal and infant ECG's will be done to characterize any arrhythmogenic disturbances caused by maternal domperidone use. Mothers will also be monitored for symptoms of arrhythmia which, if reported, will trigger additional immediate work-up including repeat ECG, the results of which will be reported in the study. The results of EMPOWER will hopefully provide evidence-based data regarding domperidone's safety (for both mother and baby) when prescribed at 30 mg/day as a galactogogue for mothers of preterm infants in the NICU, although here too, the sample size is insufficient to detect an increased risk of torsade de pointes or other ventricular arrhythmias.

There remain significant gaps in our knowledge and understanding of domperidone's effects on lactating mothers. This consensus group therefore strongly encourages further research looking at domperidone's use in lactating mothers. Particularly useful would be a randomized controlled trial to determine the relative efficacy of lower vs higher dose domperidone on breastfeeding success. Such a study would help justify whether or not there is a true need to titrate the dosage higher in mothers not responding adequately to 30 mg/day, and would be done in the out-patient setting. To address safety and low prevalence outcomes such as ventricular arrhythmias, it would also be worthwhile studying large pharmaco-epidemiologic databases (like the General Practice Research Database in the U.K.) that include large numbers of healthy lactating women. Databases of this magnitude can lend sufficiently robust power to better address low prevalence risks such as Torsade de Pointe.

Conclusion

Domperidone has a three-decade track record of use as a galactogogue to support breastfeeding mother/baby dyads. Importantly, to date, Health Canada has not received any reports of cardiac-related deaths in women taking Domperidone[35]. Furthermore, the recent Health Canada-endorsed advisory, and the studies to which it refers, are neither compelling nor specific to breastfeeding mothers. Therefore, there is strong consensus among the experts in this group that the advisory does not present valid arguments to justify changing the long established domperidone prescribing practices among lactation physicians across Canada.

There is consensus among the experts in this group that domperidone, when appropriately prescribed, improves breastfeeding outcomes. However, this group does recognize that the above is largely based on expert opinion. As such, further studies designed to yield higher-level evidence are strongly encouraged to further explore this relationship.

Until the results of further research become available, healthcare practitioners should consider the following recommendations when prescribing domperidone to breastfeeding mothers:

1. Prior to considering prescribing domperidone, ensure that there is a persistent breastfeeding problem despite an adequate trial of intensive non-pharmacologic lactation support. This would include assessment and support from a lactation consultant.

2. Screen mothers for comorbid medical conditions (including a significant personal or family history of cardiac arrhythmia), the use of QT-prolonging medications, and drugs that may affect the activity and/or metabolism of domperidone.

3. Adequately discuss the risks and benefits of domperidone's use as a galactogogue to ensure that patients make an informed decision.

4. Prescribe domperidone at the lowest effective dose and titrate up as needed based on the mother's and/or the baby's response.

5. While a patient is on domperidone, ensure regular follow-up to monitor closely for efficacy, side effects and adverse reactions.

In conclusion, the health risks to baby and mother associated with not breastfeeding are significant, well described in the medical literature, and supported by high quality scientific studies: [11-34]. The unlikely life-threatening risks associated with taking domperidone are theoretical and not well supported by the scientific literature as it relates to the lactating patient. Considering the balance of medical risks and benefits to the mother and baby, the breastfeeding experts in this group feel that the Health Canada-endorsed advisory should be viewed with caution as it relates to the lactating population. The important health benefits that breastfeeding confers to both the mother and her baby outweigh the theoretical risk associated with domperidone's use.

References

1. da Silva O, Knoppert D, Angelini M, Forret P. Effect of domperidone on milk production in mothers of premature newborns: a randomized, double-blind, placebo-controlled trial. CMAJ 2001;164(1):17-21

2. Rossi M, Giorgi G. Domperidone and long QT syndrome. Curr Drug Saf. 2010 Jul 2;5(3):257-62.

3. Keady S. Update on drugs for gastro-oesophageal reflux disease. Arch Dis Child Educ Pract Ed. 2007 Aug;92(4):ep114-8.

4. Hale T. Pharmacology Review: Drug Therapy and Breastfeeding: Pharmacokinetics, Risk Factors, and Effects on Milk Production. Neoreviews 2004. April; 5(4): e164-e172.

5. Yee Guan Yap, A John Camm. Drug induced QT prolongation and torsades de pointes. Education in Heart. Heart 2003;89:1363-1372 doi:10.1136/heart.89.11.1363

6. Roussak JB, Carey P, Parry H. Cardiac arrest after treatment with intravenous domperidone. BMJ (Clin Res Ed) 1984;289:1579.

7. FDA Talk Paper: FDA Warns Against Women Using Unapproved Drug, Domperidone, to Increase Milk Production. 2004 June 07 <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm173886.htm>

8. da Silva O, Knoppert D. Domperidone for lactating women. CMAJ 2004; 171 (7), 725-726.

9. Gabay MP. Galactogogues: medications that induce lactation. J Hum Lact. 2002 Aug;18(3):274-9.

10. Mathivanan M. Health Canada Endorsed Important Safety Information on Domperidone Maleate. 2012 Mar 2 <http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/advisories-avis/prof/2012/domperidone_hpc-cps-eng.pdf>

11. Alm B, Weenergren G, Norvenius SG, et al. Breastfeeding and the sudden infant death syndrome in Scandinavia 1992-95. Arch Dis Child 2002;86:400-2

12. Bachrach VRG, Schwarz E, Bachrach LR. Breastfeeding and the risk of hospitalization for respiratory disease in infancy. Arch Pediatr Adolesc Med. 2003;157:237-243

13. Bernier MO, Plu-Bureau G, Bossard N, et al. Breastfeeding and breast cancer: a metanalysis of published studies. Hum Reprod Update 2000;6:374-86

14. Bloch AM, Mimouni D, Minouni M, Gdalevich M. Does breastfeeding protect against allergic rhinitis during childhood? A meta-analysis of protective studies. Acta Paediatr 2002;91:275-9

15. Chen A, Rogan WJ. Breastfeeding and the risk of postneonatal death in the United States. Pediatrics 2004;113:e435-e435

16. Cunningham AS, Jelliffe DB, Jelliffe EFP. Breastfeeding and health in the 1980's: a global epidemiologic review. J Pediatr 1991;118:659-66

17. Davis MK, Savitz DA. Graubard BI. Infant feeding and childhood cancer. Lancet 1988;2:365-8

18. Fewtrell MS. The long-term benefits of having been breastfed. Current Paediatrics 2004;14:97-103

19. Freudenheim JL, Marshall JR, Graham S, Laughlin R, Vena JE, Bandera E, et al. Exposure to breastmilk in infancy and the risk of breast cancer. Epidemiology 1994;5:324-31

20. Gdlavevich M, Minouni D, Minouni M. Breastfeeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. J Pediatr 2001;139:261-6

21. Klement E, Cohen RV, Boxman J, et al. Breastfeeding and risk of inflammatory bowel disease: a systematic review with meta-analysis. Am J Clin Nutr 2004;80:1342-52

22. Kramer MS, Chalmers B, Hodnett ED, Sevkovskaya Z, Dzikovich I, Shapiro S, et al. Promotion of breastfeeding intervention trial. JAMA 2001;285:413-20

23. Kramer MS. Do breastfeeding and delayed introduction of solid foods protect against subsequent obesity? J Pediatr 1981;98:883-7

24. Lanting CI, Fidler V, Huisman M, Touwen BCL, Boersma ER. Neurological differences between 9 year old children fed breastmilk or formula milk as babies. Lancet 1994;344:1319-22

25. Lawlor DA, Riddoch CJ, Page AS, et al. Infant feeding and components of the metabolic syndrome: findings from the European youth heart study. Arch Dis Child 2005;90:582-8

26. Oddy WH. Breastfeeding protects against illness and infection in infants and children: a review of the evidence. Breastfeeding Review 2001;9(2):11-18

27. Ravelli ACJ, van der Meulen JHP, Osmond C, et al. Infant feeding and adult glucose tolerance, lipid profile, blood pressure and obesity. Arch Dis Child 2000;82:248-52

28. Rey J. Breastfeeding and cognitive development. Acta Paed Supp 2003;442:11-18

29. Sadauskaite-Kuehne V, Ludvigsson J, Padaiga, Z. Longer breastfeeding is an independent protective factor against development of type 1 diabetes mellitus in childhood. Diabetes/Metabolism Research and Reviews. 2004;20:150-7

30. Scariati PD, Grummer-Strawn LM, Fein SB. A longitudinal analysis of infant morbidity and the extent of breastfeeding in the United States. Pediatrics 1997;99:e5

31. Stuebe A, Rich-Edwards JW, Willett WC, et al. Duration of Lactation and Incidence of Diabetes type 2. JAMA 2005;294:2601-10

32. Viennemann MM, Does breastfeeding reduce the risk of sudden infant death syndrome? Pediatrics 2009;123(3):e406-e410

33. Walker M. A fresh look at the risks of artificial feeding. J Hum Lact 1993;9:97-107

34. Zhang M, Xie X, Lee AH, Binns CW. Prolonged lactation reduces ovarian cancer risk in Chinese women. Eur J Cancer Prev 2004;13:499-502

35. Written Correspondence with Health Canada. April 2012.

36. van Noord C et al. Domperidone and ventricular arrhythmia or sudden cardiac death: a population-based case-control study in the Netherlands. Drug Saf. 2010 Nov 1; 33(11): 1003-1014.

37. Johannes CB et al. Risk of serious ventricular arrhythmia and sudden cardiac death in a cohort of users of domperidone: a nested case-control study. Pharmacoepidemiol Drug Saf. 2010 Sep; 19(9): 881-888.