The Galactogogue Bandwagon

Philip O. Anderson

J Hum Lact 2013 29: 7

DOI: 10.1177/0890334412469300

This version has been modified from the version printed in the February 2013 issue of JHL (29:1). Several of the author's requested corrections were not incorporated into the prior version, and this version has been revised to include all.

Commentary

International Lactation Consultant Association
A Worldwide Network of Lactation Professionals

The Galactogogue Bandwagon

Journal of Human Lactation
29(1) 7–10

DOI: 10.1177/0890334412469300
http://jhl.sagepub.com
SAGE

Philip O. Anderson, PharmD[1]

Keywords

breastfeeding, domperidone, galactogogues, insufficient milk supply, milk production, pharmacology

A recent survey of midwives in Switzerland and Canada found that almost all used galactogogues in their practice.[1] Although Swiss midwives used predominantly oxytocin nasal spray, herbals, and homeopathic remedies, almost all the Canadian midwives used domperidone as well as herbals. Most respondents reported that they did not follow any official guideline or protocol. This issue of the *Journal of Human Lactation* (*JHL*) contains reports of 2 studies related to domperidone (originally published online by *JHL* in 2012). In 1 of these studies, researchers at an Australian hospital report that they did develop a standardized guideline for domperidone use as a galactogogue and found a large increase in use in the years after the introduction of the protocol.[2] The authors speculate that one reason for the increase might have been the dissemination of the guideline in their institution. The authors and others express concern that prescribers are using galactogogues instead of, or before, optimizing feeding techniques known to increase milk supply.[3]

A wide variety of plant products and foods have been used as galactogogues since ancient times. Recent systematic reviews found that evidence for the effectiveness of herbal galactogogues is largely lacking and that studies published to date have serious methodological errors.[4-6] More recently, synthetic pharmaceuticals have become popular, especially domperidone and metoclopramide. They increase serum prolactin, but no correlation exists between serum prolactin and milk production.[7] A meta-analysis by the Cochrane collaboration on medications to enhance milk production in mothers of preterm infants found only 2 studies worthy of inclusion, both of which used domperidone. Domperidone was deemed effective in the short-term enhancement of milk supply.[8] Another meta-analysis that also included studies on term infants found 3 valid domperidone studies, 2 of which were included in the Cochrane analysis.[9] All of these studies used a dosage of 10 mg 3 times daily for 7-14 days. The 3 studies have a combined total of fewer than 80 subjects. As a reference point, a new drug in the United States is typically studied in 500 to 3000 subjects before US Food and Drug Administration (FDA) approval and marketing.[10]

The other study in this issue of *JHL* attempts to address the gap in information on domperidone for mothers of preterm infants.[11] The study compared doses of 10 mg and 20 mg, both of which were given 3 times daily. Unfortunately, the study had too few patients and too little power to determine whether 20 mg of domperidone 3 times daily is superior to 10 mg. The results of this study are consistent with those of another study that compared domperidone dosages of 30 mg/day and 60 mg/day and failed to demonstrate a difference in milk production, although it also had too few patients to determine the effect of dose on clinical response.[12]

Galactogogue studies are difficult to perform well. Nevertheless, drug studies should be performed, analyzed, and interpreted in a scientifically sound manner before we accept that the drugs and dosages are effective and safe. A multicenter study called EMPOWER, which will include over 500 subjects,[13] should help to clarify issues of efficacy and timing of domperidone in mothers of preterm infants, but it will be a few years before results are known.

Concern also exists with the safety of higher domperidone dosages. Health Canada, the Canadian governmental agency charged with drug regulation, released a warning to health professionals on March 2, 2012 concerning an increased risk of arrhythmias and sudden cardiac death caused by prolonged QT interval in patients receiving daily domperidone dosages greater than 30 mg.[14] The warning states that domperidone should be initiated at the lowest possible dosage and that "patients should be advised to stop taking domperidone and seek immediate medical attention if they experience signs or symptoms of an abnormal heart rate or rhythm while taking domperidone. These include dizziness, palpitations, syncope or seizures." This warning refers to oral domperidone use, not the intravenous use referred to by the FDA in 2004.[15] Nursing mothers were not discussed in the Health Canada warning, because domperidone is not approved as a galactogogue in Canada or any other country.

Date submitted: September 27, 2012; Date accepted: November 2, 2012.

Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, La Jolla, CA, USA

Corresponding Author:
Philip O. Anderson, PharmD, University of California–San Diego, Skaggs School of Pharmacy and Pharmaceutical Sciences, 9500 Gilman Dr, MC 0657, La Jolla, CA 92093-0657, USA
Email: phanderson@ucsd.edu

In May 2012, a group of Canadian breastfeeding clinicians signed a consensus document on the use of domperidone.[16] The document generally reviews the use of domperidone as a galactogogue, but it focuses specifically on downplaying the Health Canada warning because of differences between the ages of nursing mothers and the patients referred to in the warning. The document states that lactation specialists in Canada prescribe domperidone "from a starting dose of 30 to 90 mg daily to a maximum dose of 80 to 160 mg daily." Note that the maximum recommended dosage in countries in which domperidone is available is 80 mg daily.[17] In this issue of *JHL*, authors studying dispensing patterns of domperidone in an Australian hospital state that domperidone should probably be used for "at least 6 weeks in order to observe its effectiveness,"[2] however, no published scientific data support a duration of use longer than 2 weeks. In fact, one study found that prolonged elevation of prolactin with a galactogogue had no beneficial effect on milk production beyond the first 2 weeks postpartum in mothers of full-term infants.[18]

Domperidone is metabolized by CYP3A4, which is inhibited by a number of substances, such as grapefruit juice, fluconazole, erythromycin, clarithromycin, and others. These agents increase maternal serum domperidone concentrations from 3- to 5-fold, which adds to the risk of prolonged QT interval and cardiac arrhythmia.[17] Concurrent drugs that cause QT prolongation can also add to the risk.[19] Even without excessive dosages or interacting substances, abdominal cramping, nausea, diarrhea, dry mouth, headache, and dizziness (see Health Canada warning) have been reported in domperidone galactogogue studies. Some of these effects were more frequent with 60 mg daily than with 30 mg daily.[11,12,20,21]

The rhetoric and clinical practices surrounding galactogogues seem to be getting ahead of the underlying science, a concern that is clear in the Australian paper describing increasing rates of prescribing at that facility.[2] The population that could benefit from galactogogues has not been clearly elucidated, nor has the safety of galactogogues been adequately demonstrated. Even the physiologic causes of low milk production are not well established. Use of domperidone and metoclopramide assumes that low milk production is caused by low serum prolactin, although some women fail to respond.[12,22-25] In Switzerland, where oxytocin nasal spray is still commercially available, targeting the oxytocin pathway is popular.[1] Some herbals used as galactogogues are partial estrogen antagonists and might target women with excessive estrogen.[26] Indeed, as the Australian researchers note,[2] galactogogue selection seems to be based more on tradition, word of mouth, and convenience than on pathophysiologic diagnosis. In some cases, the mismatch between physiology and treatment might be a cause of unwarranted dosage escalation by clinicians and mothers.

Currently, the best scientific data and expert medical opinion support the following:

1. Galactogogues should be used only after all modifiable factors that affect milk production have been addressed. Good maternal education about breastfeeding usually obviates the need for galactogogues,[27-29] and initiation of breast milk expression within the first hour postpartum may provide an increase in milk supply sufficient to avoid galactogogues in some mothers of very low birth weight infants.[30] Excellent practice guidelines have been developed by the Academy of Breastfeeding Medicine.[3]
2. Herbals and foods used as galactogogues have little or no scientific evidence of efficacy, which does not mean they are all ineffective, but they may be serving as placebos in many cases.[3] Most placebo-controlled galactogogue studies find increases in milk production in their placebo arms.[28,31,32] The identity and purity of herbals are concerns because of inadequate testing requirements.
3. Based on the minimal literature available,[8,9] domperidone likely has galactogogue activity at a dosage of 10 mg 3 times daily for 7-14 days, although the population that will benefit is poorly defined. The starting dosage should not exceed 30 mg daily; higher dosages and longer durations of administration have not been scientifically demonstrated to be safe or more effective, nor has increasing the dosage in nonresponders been shown to be more effective than 30 mg per day.
4. Domperidone poses minimal risk to the nursing infant, but some mothers experience annoying side effects. The risk of cardiac arrhythmias in young women may be lower than in older patients, but it is unlikely to be zero. High dosages, concurrent use of some common drugs, and preexisting cardiac disease may increase the risk,[19] so mothers should be warned of possible cardiac side effects. Domperidone is not likely to be commercially available in the United States in the near future, if ever, and potential safety hazards are associated with purchasing drugs on the Internet.
5. Metoclopramide might have efficacy similar to that of domperidone,[21,33,34] but maternal depression and tardive dyskinesia are concerns with prolonged use. Metoclopramide also results in greater infant drug exposure and risk of side effects than domperidone.[35]

All breastfeeding professionals wish to help mothers who have a low milk supply, but low milk supply is not a clear-cut diagnosis with a single cause. It may even be a misperception by the nursing mother that requires only reassurance. Most important is whether an increase in milk supply will make a difference in infant outcomes, such as adequacy of weight gain and reduced use of supplements. A small increase in milk

supply might be important for a preterm infant, but the same increase may be irrelevant for an older infant.

Those who use galactogogues should do so infrequently and thoughtfully with the knowledge that evidence for their safety and efficacy is sparse. Adverse reactions to galactogogues should be reported to local or national adverse reaction monitoring agencies. More research is needed in several areas, especially maternal factors that determine response to galactogogues.

Declaration of Conflicting Interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

References

1. Winterfeld U, Meyer Y, Panchaud A, Einarson A. Management of deficient lactation in Switzerland and Canada: a survey of midwives' current practices. *Breastfeed Med*. 2012;7(4):317-318.
2. Grzeskowiak LE, Lim SW, Thomas AE, Ritchie U, Gordon AL. Audit of domperidone use as a galactogogue at an Australian tertiary teaching hospital. *J Hum Lact*. 2013;29(1):32-37.
3. The Academy of Breastfeeding Medicine Protocol Committee. ABM Clinical Protocol #9: Use of galactagogues in initiating or augmenting the rate of maternal milk secretion. First revision, January 2011. *Breastfeed Med*. 2011;6(1):41-49.
4. Zapantis A, Steinberg JG, Schilit L. Use of herbals as galactagogues. *J Pharm Pract*. 2012;25(2):222-231.
5. Budzynska K, Gardner ZE, Duguoa JJ, Low Dog T, Gardiner P. Systematic review of breastfeeding and herbs. *Breastfeed Med*. 2012;7(6):489-503.
6. Forinash AB, Yancey, Barnes KN, Myles TD. The use of galactogogues in the breastfeeding mother. *Ann Pharmacother*. 2012;46(10):1392-1404.
7. Anderson PO, Valdes V. A critical review of pharmaceutical galactagogues. *Breastfeed Med*. 2007;2(4):229-242.
8. Donovan TJ, Buchanan K. Medications for increasing milk supply in mothers expressing breastmilk for their preterm hospitalised infants. *Cochrane Database Syst Rev*. 2012; 3CD005544.
9. Osadchy A, Moretti ME, Koren G. Effect of domperidone on insufficient lactation in puerperal women: a systematic review and meta-analysis of randomized controlled trials. *Obstet Gynecol Int*. 2012;2012:642893.
10. Strom BL. What is pharmacoepidemiology? In: Strom BL, Kimmel SE, Hennessy S, eds. *Pharmacoepidemiology*. 5th ed. Chicester, UK: John Wiley & Sons. 2012:12.
11. Knoppert DC, Page A, Warren J et al. The effect of two different domperidone doses on maternal milk production. *J Hum Lact*. 2013;29(1):38-44.
12. Wan EW, Davey K, Page-Sharp M, Hartmann PE, Simmer K, Ilett KF. Dose-effect study of domperidone as a galactagogue in preterm mothers with insufficient milk supply, and its transfer into milk. *Br J Clin Pharmacol*. 2008;66(2):283-289.
13. Asztalos EV, Campbell-Yeo M, Dasilva OP, Kiss A, Knoppert DC, Ito S. Enhancing breast milk production with domperidone in mothers of preterm neonates (EMPOWER trial). *BMC Pregnancy Childbirth*. 2012;12(1):87.
14. Health Canada endorsed important safety information on domperidone maleate. March 2, 2012. http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2012/domperidone_hpc-cps-eng.php. Accessed October 10, 2012.
15. FDA warns against women using unapproved drug, domperidone, to increase milk production. FDA Talk Paper. June 7, 2004. http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm173886.htm. Accessed October 10, 2012.
16. Flanders D, Lowe A, Kramer M, et al. A consensus statement on the use of domperidone to support lactation. http://www.ilca.org/files/CLCA/PDF/Listserv%20pdfs/Domperidone%20Consensus%20Statement%20Final%20May%2011%202012.pdf. Accessed October 10, 2012.
17. Domperidone. In: Sweetman S, ed. *Martindale: The Complete Drug Reference* [Internet database]. Greenwood Village, CO: Thomson Micromedex. Accessed October 10, 2012.
18. BarguZo JM, del Pozo E, Cruz M, Figueras J. Failure of maintained hyperprolactinemia to improve lactational performance in late puerperium. *J Clin Endocrinol Metab*. 1988;66(4): 876-879.
19. Bozzo P, Koren G, Ito S. Health Canada advisory on domperidone: should I avoid prescribing domperidone to women to increase milk production? *Can Fam Physician*. 2012;58(9): 952-953.
20. Jantarasaengaram S, Sreewapa P. Effects of domperidone on augmentation of lactation following cesarean delivery at full term. *Int J Gynaecol Obstet*. 2012;116(3):240-243.
21. Ingram J, Taylor H, Churchill C, Pike A, Greenwood R. Metoclopramide or domperidone for increasing maternal breast milk output: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed*. 2012;97(4):F241-245.
22. Gupta AP, Gupta PK. Metoclopramide as a lactogogue. *Clin Pediatr (Phila)*. 1985;24(5):269-272.
23. Ehrenkranz RA, Ackerman BA. Metoclopramide effect on faltering milk production by mothers of premature infants. *Pediatrics*. 1986;78(4):614-620.
24. Toppare MF, Laleli Y, Senses DA, Kitapci F, Kaya IS, Dilmen U. Metoclopramide for breast milk production. *Nutr Res*. 1994;14:1019-1029.
25. Fife S, Gill P, Hopkins M, Angello C, Boswell S, Nelson KM. Metoclopramide to augment lactation, does it work? A randomized trial. *J Matern Fetal Neonatal Med*. 2011;24(11): 1317-1320.
26. Buddha S, Noffke B, Brown D, Westerhoff M. Breast feeding, hypogalactia and molecular exploration of herbal galactogogues [abstract]. *Planta Med*. 2012;78(11):1059.
27. Seema, Patwari AK, Satyanarayana L. Relactation: an effective intervention to promote exclusive breastfeeding. *J Trop Pediatr*. 1997;43(4):213-216.

28. Hansen WF, McAndrew S, Harris K, Zimmerman MB. Metoclopramide effect on breastfeeding the preterm infant: a randomized trial. *Obstet Gynecol*. 2005;105(2):383-389.
29. Sakha R, Behbahan AG. Training for perfect breastfeeding or metoclopramide: which one can promote lactation in nursing mothers? *Breastfeed Med*. 2008;3(2):120-123.
30. Parker LA, Sullivan S, Krueger C, Kelechi T, Mueller M. Effect of early breast milk expression on milk volume and timing of lactogenesis stage II among mothers of very low birth weight infants: a pilot study. *J Perinatol*. 2012; 32(3):205-209.
31. da Silva OP, Knoppert DC. Domperidone for lactating women. *CMAJ*. 2004;171(7):725-726.
32. Campbell-Yeo ML, Allen AC, Joseph KS et al. Effect of domperidone on the composition of preterm human breast milk. *Pediatrics*. 2010;125(1):e107-114.
33. Brouwers JR, Assies J, Wiersinga WM, Huizing G, Tytgat GN. Plasma prolactin levels after acute and subchronic oral administration of domperidone and of metoclopramide: a cross-over study in healthy volunteers. *Clin Endocrinol (Oxford)*. 1980;12(5):435-440.
34. Brown TE, Fernandes PA, Grant LJ, Hutsul JA, McCoshen JA. Effect of parity on pituitary prolactin response to metoclopramide and domperidone: implications for the enhancement of lactation. *J Soc Gynecol Investig*. 2000;7(1):65-69.
35. The United States National Library of Medicine. Metoclopramide. http://lactmed.nlm.nih.gov. Accessed October 10, 2012.

International Lactation Consultant Association
A Worldwide Network of Lactation Professionals

Erratum

Journal of Human Lactation
XX(X) 1

DOI: 10.1177/0890334413479947
jhl.sagepub.com
SAGE

Anderson, PO. The galactogogue bandwagon. *J Hum Lact*. 2013;29(1):7-10. (Original doi: 10.1177/0890334412469300)

In the above-referenced commentary, the mention of the EMPOWER study on page 7 should have indicated a future tense, as the study has not yet occurred (as of time of publication). The corrected sentence is as follows:

> A multicenter study called EMPOWER, which will include over 500 subjects,[13] should help to clarify issues of efficacy and timing of domperidone in mothers of preterm infants, but it will be a few years before results are known.

Also, references 2 and 11 should have been updated to reflect their inclusion within the same February 2013 issue. The corrected references are as follows:

2. Grzeskowiak LE, Lim SW, Thomas AE, Ritchie U, Gordon AL. Audit of domperidone use as a galactogogue at an Australian tertiary teaching hospital. *J Hum Lact*. 2013;29(1):32-37.
11. Knoppert DC, Page A, Warren J et al. The effect of two different domperidone doses on maternal milk production. *J Hum Lact*. 2013;29(1):38-44.

The online version of this article, available at http://jhl.sagepub.com/content/29/1/7, has been updated to reflect these corrections.