

The Effect of 2 Different Domperidone Doses on Maternal Milk Production

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Background

Breastmilk - Benefits

○ Recommended for first 6 months of life (CPS, AAP)

“Human milk is the preferred feeding for all infants, including premature and sick newborns with rare exceptions...”



AAP Policy on Breastfeeding and the Use of Human Milk, 1997.

Breastfeeding Advantages

- Breast milk : hormones, growth factors, cytokines, living cells and immunoglobulins
- Preterm infants fed human milk have:
 - Faster achievement of full enteric feeding
 - Decreased frequency and severity of infections
 - Enhanced retinal development, visual acuity and neuro-cognitive outcomes


Mothers of Premature Babies

- 3 times at risk of not producing an adequate milk supply


Mothers of Premature Babies

- 3 times at risk of not producing an adequate milk supply
 - Absence of suckling
 - Stress

The Challenges of Preterm Breastfeeding



Mothers are capable of producing milk for any viable infant, however, there are many challenges to overcome...



Premature birth is unexpected and having a baby in the NICU places many stresses on mothers and families.



Preterm infants are not mature enough to co-ordinate oral feeding until they are 32-35 weeks gestational age. They are not strong enough to maintain a milk supply until 36-46 weeks post-conception.



Preterm mothers must use a breast pump 8-10 times/24 hrs to artificially stimulate their milk supply. Pumps mimic the term infant at the breast but are not as efficient and do not provide the same psychological stimulus.

Domperidone

- Peripherally acting dopamine antagonist
- Official use : prokinetic drug
- Side effect : increase in prolactin
- Galactagogue (Canada, Europe, Australia)
- NOT in USA
- 2004 FDA warning

Domperidone as a Galactagogue

Mean Daily Milk Production

- > Domperidone (44.5%) vs placebo (+16.6%) ($p = 0.05$)

Serum Prolactin (Day 5)

- > Domperidone (119.3 $\mu\text{g/L}$) vs placebo 18.1 $\mu\text{g/L}$, $p = 0.008$)

CMAJ 2001;164:17-21

Continuing Uncertainty...

- Optimal dosage / duration not known
- Vary widely between physicians
- No studies of long term efficacy or safety

FDA U.S. Food and Drug Administration Department of Health and Human Services

FDA Warns Against Women Using Unapproved Drug, Domperidone, to Increase Milk Production

In response to reports that women may be using an unapproved drug, domperidone, to increase milk production (lactation), the Food and Drug Administration (FDA) is **warning breastfeeding women not to use this product** because of safety concerns. Today, FDA also **issued six letters to pharmacies that compound products** containing domperidone and firms that supply domperidone for use in compounding.

June 2004

Thomas Hale
“Medication and Mother’s Milk”

○ “...This warning from the FDA has nothing to do with its safety. It’s all about the importation of drugs from Canada and control by this federal agency.”



UK Response

Cardiac adverse effects were reported with the parenteral formulation and led to its withdrawal; however they are not listed as a problem with oral administration, which is considered sufficiently safe for domperidone tablets to be available OTC for adult use.



Canadian Response

○ CMAJ 28 September 2004



FDA Rationale ?

- Cardiac arrhythmias, cardiac arrest and sudden death following IV domperidone
- Early to mid 1980s : case reports
- High doses in patients receiving chemotherapy

The Facts

- Ventricular fibrillation and death in a 69 year old patient (bolus of 5.7 mg/kg, infusion of 7.7 mg/kg over 13 hours)⁽¹⁾
- Sudden death in 2/46 patients who received 2 mg/kg IV domperidone⁽²⁾
- Ventricular arrhythmias in 4/4 patients (20 to 50mg, IV); all were hypokalemic⁽³⁾

1. *Lancet* 1982;1:1019. 2. *Lancet* 1984;2:1336-7. 3. *BMJ Clin Res Ed* 1984;289:1579.

Pharmacokinetics

- Oral bioavailability 13-17 %
- Mean peak serum concentration following 10 mg/kg in healthy volunteers
 - 590 ng/mL immediately following rapid IV administration
 - 23 ng/mL 30 minutes after oral administration

European Journal of Drug Metabolism and Pharmacokinetics 1981;6:61-70.

Pharmacokinetics

- 40, 80 and 160 mg/day, po, resulted in mean SS C_{max} of 11, 13.9 and 14.1 ng/mL

Pharmacotherapy 1990;16:253 (Abstract # 149)

**Domperidone
and QT_C Interval**

- Isolated guinea pig hearts
- Significant prolongation of cardiac re-polarization at 42 ng/mL
- Clinical increase in QT_C interval ?

Circulation 2000;102:1883-5

Take Home Message

- Potential for effect on QT_C interval with high serum concentrations
- Be wary of potential drug interactions
 - Inhibition of QT_C (eg quinolones)
 - Inhibition of CYP3A4 (eg fluconazole)
- Family history of arrhythmias

Domperidone as a Galactagogue: Limited Investigations

- 10mg and 20mg dosing ⁽¹⁾
 - Crossover study in 4 patients
 - Increased milk production, but no difference between doses detected
- Milk composition ⁽²⁾
 - 10mg po tid x 14 days
 - No substantial changes in nutrient composition of milk

⁽¹⁾ Wan Br J Clin Pharmacol 2008;66:283-9
⁽²⁾ Campbell-Yeo Pediatrics 2010;125(1):e107-14.

Purpose

- To determine an optimal dosage of domperidone as a galactagogue

Primary Objective

- To determine if milk production is greater in mothers of premature newborns who take 20 mg domperidone times daily compared to 10 mg domperidone three times daily for 28 days.

Secondary Objectives

- To measure domperidone concentrations in serum and breast milk.
- To measure serum prolactin response.
- To determine the area under the curve (AUC) milk/plasma ratio for domperidone
- To identify any adverse effects in mothers or their preterm infants that may be related to the use of Domperidone.

Methods

Inclusion Criteria

- Identified by NICU lactation consultants
- Mother of singleton or multiples who were < 33/52 gestation
- Maternal age 18 to 45 years
- Daily milk volume <500 mL at postpartum day 14-21

Exclusion Criteria

- Maternal history of breast surgery, breast cancer, chronic debilitating disease or endocrine disorder
- Family history of a clinically recognized arrhythmia
- Receiving an antiarrhythmic drug, a quinolone or a drug metabolized by CYP3A4 (eg, ketoconazole, macrolide)
- Mothers of infants who developed NEC

Randomization

- Computer generated list, blocks of 2 and 4
- Cards in sealed envelopes kept in Pharmacy
- Domperidone 10mg OR 20mg three times daily
 - 4 weeks @ 3 times daily
 - 1 week @ 2 times daily
 - 1 week @ once daily

Tablets and Placebo

- Domperidone tablets and identical placebo supplied by Apotex Inc (Weston, ON)
- Each subject received 2 vials of tablets
 - 10mg domperidone
 - 10mg domperidone OR placebo

Subjects

- Ameda electric breast pumps used to initiate lactation
- Pumping 8 to 10 times per 24 hours
- Milk production recorded for entire 6 weeks
- Medication ingestion recorded

Blood Work

- Day "0"
 - Baseline prolactin
- Day 10 – 15
 - Breastmilk and blood (4 samples) collected over 8 hours

Statistics

- Sample size of 10 subjects per group required to detect difference of 50mL in milk volume between groups
- Repeated measures ANOVA used for primary research question

Analyses

- Domperidone
 - Serum and breast milk
 - HPLC/mass spectrometry
- Prolactin
 - Automated immunoassay analyzer (Advia Centaur)

Results

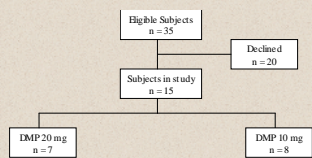


Figure 1. Study flow diagram. DMP- domperidone

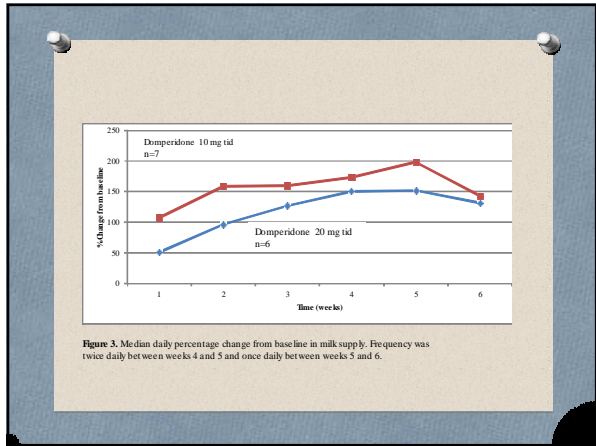


Figure 3. Median daily percentage change from baseline in milk supply. Frequency was twice daily between weeks 4 and 5 and once daily between weeks 5 and 6.

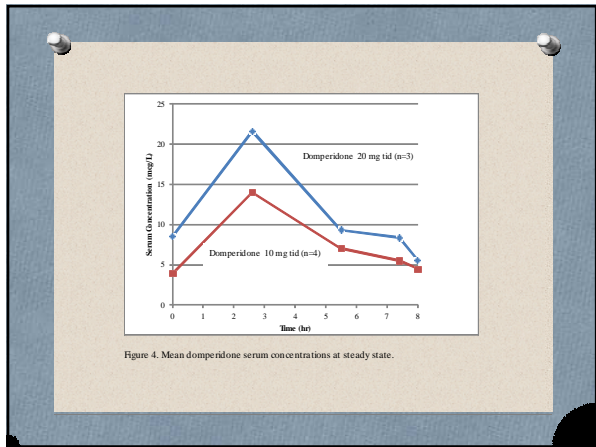


Figure 4. Mean domperidone serum concentrations at steady state.

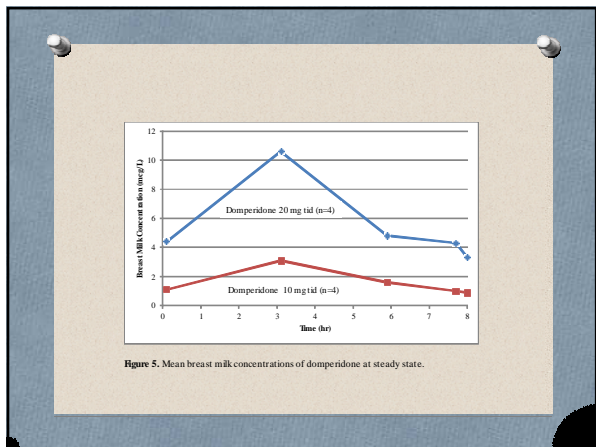


Figure 5. Mean breast milk concentrations of domperidone at steady state.

Table 2. Steady state serum and breast milk (bm) AUC and AUC_{bm} / AUC_{serum} values for 8 hours following the administration of domperidone (Mean \pm SD).

| | Domperidone 20mg (n=3) | Domperidone 10mg (n=4) |
|---|---------------------------|---------------------------|
| AUC _{serum} \pm SD mcg.h/L | 101.8 \pm 88 | 67.4 \pm 42.3 |
| AUC _{bm} \pm SD mcg.h/L | 50.1 \pm 36.5 | 15.3 \pm 6.9 |
| AUC _{bm} / AUC _{serum} \pm SD | 0.5 \pm 0.6 <i>↗</i> | 0.4 \pm 0.4 <i>↗</i> |

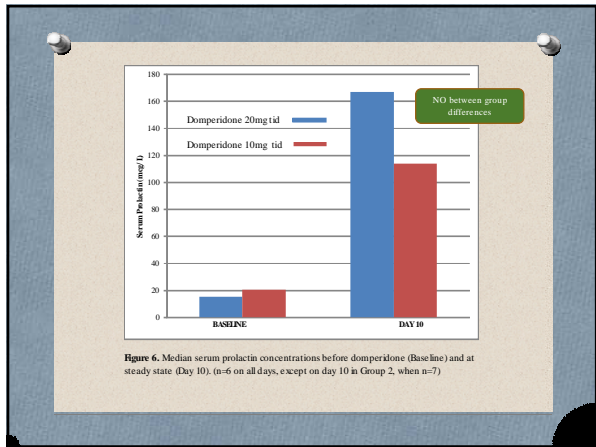


Figure 6. Median serum prolactin concentrations before domperidone (Base line) and at steady state (Day 10). (n=6 on all days, except on day 10 in Group 2, when n=7)

Discussion

Discussion

- First study to examine 2 different doses, incl tapering dose, over 6 week period
- Demonstrated stat sig, progressive increase in milk production, for fist 4 weeks
- Between group difference NS, but clinically significant (300 mL difference by week 4)

Conclusions

- 1) An increased dose of domperidone produces a clinically significant increase in milk supply. Our results likely failed to reach statistical significance due to a low number of subjects.
- 2) Twice daily dosing of domperidone may be adequate to produce clinically relevant increases in breast milk.

Future Studies

- Is twice daily dosing adequate ?
- What is the optimal duration of therapy with domperidone ?
- Are increased doses and prolonged duration of domperidone therapy safe to mother and baby ?

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