Effect of Domperidone on the Composition of Preterm Human Breast Milk

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KEY WORDS

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WHAT'S KNOWN ON THIS SUBJECT: Domperidone, a dopamine antagonist, has been shown to increase breast milk volume. Mothers of preterm infants are increasingly prescribed domperidone to augment breast milk supply, but its effect on the nutrient levels in breast milk has yet to be studied.

WHAT THIS STUDY ADDS: We demonstrate that domperidone significantly increases preterm mother's breast milk volume without altering the nutrient composition of breast milk.

abstract

OBJECTIVE: Domperidone is increasingly prescribed to improve breast milk volume despite a lack of evidence regarding its effects on breast milk composition. We examined the effect of domperidone on the nutrient composition of breast milk.

PATIENTS AND METHODS: Forty-six mothers who had delivered infants at <31 weeks' gestation, who experienced lactation failure, were randomly assigned to receive domperidone or placebo for 14 days. Protein, energy, fat, carbohydrate, sodium, calcium, and phosphate levels in breast milk were measured on days 0, 4, 7, and 14, serum prolactin levels were measured on days 0, 4, and 14, and total milk volume was recorded daily. Mean within-subject changes in nutrients and milk volumes were examined.

RESULTS: Maternal and infant characteristics, serum prolactin level, and breast milk volume and composition were not significantly different between domperidone and placebo groups on day 0. By day 14, breast milk volumes increased by 267% in the domperidone-treated group and by 18.5% in the placebo group ($P = .005$). Serum prolactin increased by 97% in the domperidone group and by 17% in the placebo group ($P = .07$). Mean breast milk protein declined by 9.6% in the domperidone group and increased by 3.6% in the placebo group ($P = .16$). Changes in energy, fat, carbohydrate, sodium, and phosphate content were also not significantly different between groups. Significant increases were observed in breast milk carbohydrate (2.7% vs −2.7%; $P = .05$) and calcium (61.8% vs −4.4%; $P = .001$) in the domperidone versus placebo groups. No significant adverse events were observed among mothers or infants.

CONCLUSION: Domperidone increases the volume of breast milk of preterm mothers experiencing lactation failure, without substantially altering the nutrient composition. *Pediatrics* 2010;125:e107–e114

Breast milk is generally considered to be the optimal form of nutrition for all infants, and increasingly, mothers of infants being cared for in NICUs are asked to provide expressed breast milk.[1,2] However, mothers of very preterm infants often find it difficult to provide adequate quantities of expressed breast milk to meet their infant's needs over prolonged periods of time, despite appropriate lactation counseling and the use of nonpharmacologic strategies.[3–9] Consequently, medications such as domperidone and metoclopramide are often recommended.[10]

Domperidone, a gastric motility agent, is used as a galactagogue (off-label) in many countries including Australia, Belgium, Canada, Ireland, Italy, Japan, the Netherlands, and the United Kingdom. In 2004, the US Food and Drug Administration issued a warning[11] that breastfeeding women not use domperidone because of an increased risk of cardiac arrhythmia and sudden death observed in patients with cancer with low serum potassium who were receiving high-dose intravenous domperidone therapy concurrently with chemotherapy.[12,13] Several letters to the editor[14–16] that followed the US Food and Drug Administration directive rebutted the warning and emphasized the evidence showing the safety of domperidone in lactating mothers.

Domperidone, acting as an antidopaminergic, increases prolactin concentration and augments lactation. As a prokinetic agent, the maximum approved oral dose of domperidone is 20 mg given 4 times per day, and transient adverse effects reported include abdominal cramps, dry mouth, and headache.[17] As a galactagogue, 2 smaller dosing strategies of domperidone (10 mg or 20 mg 3 times daily) have been explored by the authors of 3 studies involving mothers of term[18] and preterm[19,20] infants. None of these authors reported any adverse effects in either the mother or the infant apart from abdominal cramping in 1 mother receiving the higher dose.[20] Domperidone does not readily cross the blood brain barrier and is minimally secreted into breast milk.[21–24]

Galactagogues such as metoclopramide have been linked to accelerated declines in the protein concentration of breast milk and also to changes in the electrolyte composition of breast milk.[25,26] No author has examined the effect of domperidone on the breast milk composition. Given the importance of nutrition for very preterm infants and the need for pharmacologic methods to support lactation in mothers of preterm infants, we conducted a randomized, double-blind, placebo-controlled trial of the effect of domperidone on the nutrient composition of breast milk among mothers of very preterm infants.

PATIENTS AND METHODS

Study Setting and Population

A detailed description of the study design has been published previously.[27] In brief, the study was conducted in a tertiary level NICU at the IWK Health Centre in Halifax, Nova Scotia, Canada. The study was approved by the ethics review board of the IWK Health Centre and the National Health Board (No. 093770). Written informed consent was obtained from all participants before study enrollment. Between October 2003 and November 2007, we enrolled mothers who had delivered infants at <31 weeks' gestation, who were mechanically expressing breast milk by using a double collecting system, and who experienced lactation failure ≥ 3 weeks after delivery. Lactation failure was defined by at least 1 of the following criteria: (1) a decreasing milk supply by $>30\%$ from peak volume (based on maternal account); and (2) inability to provide adequate breast milk to meet the daily nutritional intake of their infant. Mothers were considered ineligible if they (1) were taking medication known to alter the effect of domperidone (eg, ranitidine) or interact with it (eg, haloperidol), (2) were experiencing mastitis, (3) had a chronic illness, (4) had previous breast surgery, (5) had known lactose intolerance, or (6) were already taking domperidone.

Study Outcomes

The primary outcome was the within-subject change in breast milk protein concentration. Secondary outcomes included within-subject changes in fat, carbohydrate, lactose, energy, calcium, phosphate, and sodium content of breast milk. Within-subject change was first calculated [(individual's day 14 value $-$ individual's day 0 value) $\times$ 100/individual's day 0 value] and the mean within-subject change in each group was then determined. Other outcomes of interest included daily breast milk volume, serum prolactin concentration, and breastfeeding rates 2 weeks after treatment completion and at discharge. Change in daily breast milk volume was calculated as both a mean within-subject change and as a change in the mean of the group [eg, for the domperidone group: (mean day 14 volume $-$ mean day 0 volume) $\times$ 100/mean day 0 volume)].

Study Design and Intervention

Eligible and consenting women were randomly assigned by using a computer-based code in blocks of 4, known only to off-site pharmacy staff, to receive domperidone (10 mg orally, 3 times daily)[19] or placebo for a 2-week period. Mothers of infants ≥ 3 but <4 weeks after delivery were stratified and randomly assigned separately from those mothers of infants ≥ 4 weeks after delivery. Domperidone tablets were crushed and mixed with lactose by pharmacy staff and placed

in clear capsules. Plain lactose powder was placed in clear capsules to act as the placebo, with these capsules made identical in appearance to the domperidone capsules. Participants received their 2-week drug or placebo supply after they were randomly assigned. Participants were provided with instructions related to self-administration, and were asked to return the medication vial and any unused medication at the completion of the 2-week period. The study nurse (blinded to treatment allocation) had daily contact with each participant and was able to review instructions and identify possible adverse effects. All infants underwent cardiorespiratory monitoring throughout the study, and their charts were reviewed daily for any adverse events.

Baseline measurements were taken and recorded after randomization (day 0). Mothers were asked to express their milk according to the standard NICU practice. Each participant was provided a double-pump collecting system (Symphony Breast Pump, Medela, Mississauga, Ontario, Canada), sterile collection bottles, and was instructed to collect 24-hour samples of breast milk for the day before beginning treatment and then each day for the 2-week period. Mothers were requested to record the amount of milk pumped, the date and time, and to ensure that adhesive labels with this information were placed on each of the containers. A new container was used for each pumping and daily milk volumes were calculated. On days 0, 4, 7, and 14, 2 small samples (1 and 30 mL) of milk from a pooled 24-hour collection were retained for analysis. The remainder of the milk was made available for the infant as usual.

Breast milk samples (30 mL volume) were frozen (−70°C) and couriered in batches of 8 for chemical analysis of macronutrient content. Total nitrogen was determined by using the Kjeldahl method[28]; fat was determined by using the Roese-Gottlib method; ash and moisture were determined by using the forced air oven method[29]; and, energy and carbohydrate concentration were calculated by differences remaining when measured content was subtracted from total weight by using standardized methods.[30] Analysis of micronutrient content was conducted on-site (1 mL volume). Phosphate content was measured by using the ammonium molybdate method on the Ortho Vitros (Ortho-Clinical Diagnostics, a division of Janssen-Ortho Inc. 2003-2009, Markham, Ontario, Canada) chemistry analyzer.[31] Calcium content was determined by using the Arseno (III) method on the Ortho Vitros (Ortho-Clinical Diagnostics, a division of Janssen-Ortho Inc. 2003-2009, Markham, Ontario, Canada) chemistry analyzer.[31] Sodium content was determined by using the ion selective electrode method.[32] Every attempt was taken to collect serum prolactin, measured on days 0, 4, and 14, before pumping breast milk.[33] Prolactin was measured by using chemiluminescence immunoassay on the Vitros Eci (Ortho-Clinical Diagnostics, a division of Janssen-Ortho Inc. 2003-2009, Markham, Ontario, Canada) analyzer.[34]

Each participant was contacted by the research nurse either in person or by telephone and was questioned regarding breast-feeding 2 weeks after completion of the study and at discharge. Subjects were also asked if they had taken domperidone after the completion of the study.

Sample Size

Sample size was calculated by using a 2-sided α error of .05 and a power of 80%. On the basis of the medical literature[35] and previous clinical understanding, 22 subjects were required per group to detect a significant ≥20% change in protein content (in the domperidone group relative to the placebo group). We also had sufficient power to detect a ≥20% change in fat content and a ≥10% change in energy content, if such differences were in fact caused by domperidone.[35]

Statistical Analysis

All analyses used an intention-to-treat approach. Blinding of group assignment was retained until the analysis was completed. Categorical data were analyzed by using χ^2 tests. Primary and secondary outcomes were analyzed by comparing the means of the within-subject change before and after treatment between the domperidone and placebo groups. *P* values were calculated to express the statistical significance of the difference between the mean within-subject change between days 0 and 14 in the domperidone group and the mean within-subject change between days 0 and 14 in the placebo group. A 2-sided *P* value of $<.05$ was considered to be statistically significant. Statistical analysis was conducted by using SAS software (SAS Institute, Inc, Cary, NC).

RESULTS

Study Groups

Of the 278 mothers of infants born at <31 weeks' gestation who were screened during the study period, 61 mothers were eligible for the study and 46 provided informed consent and were recruited (Fig 1). Of these, 22 were randomly assigned to receive domperidone and 24 to receive placebo. Most maternal and infant characteristics were not significantly different between the domperidone and placebo groups at randomization (Table 1), although differences in mean gestational age and birth weight were nominally significant ($P = .06$ and .05, respectively). The primary analysis

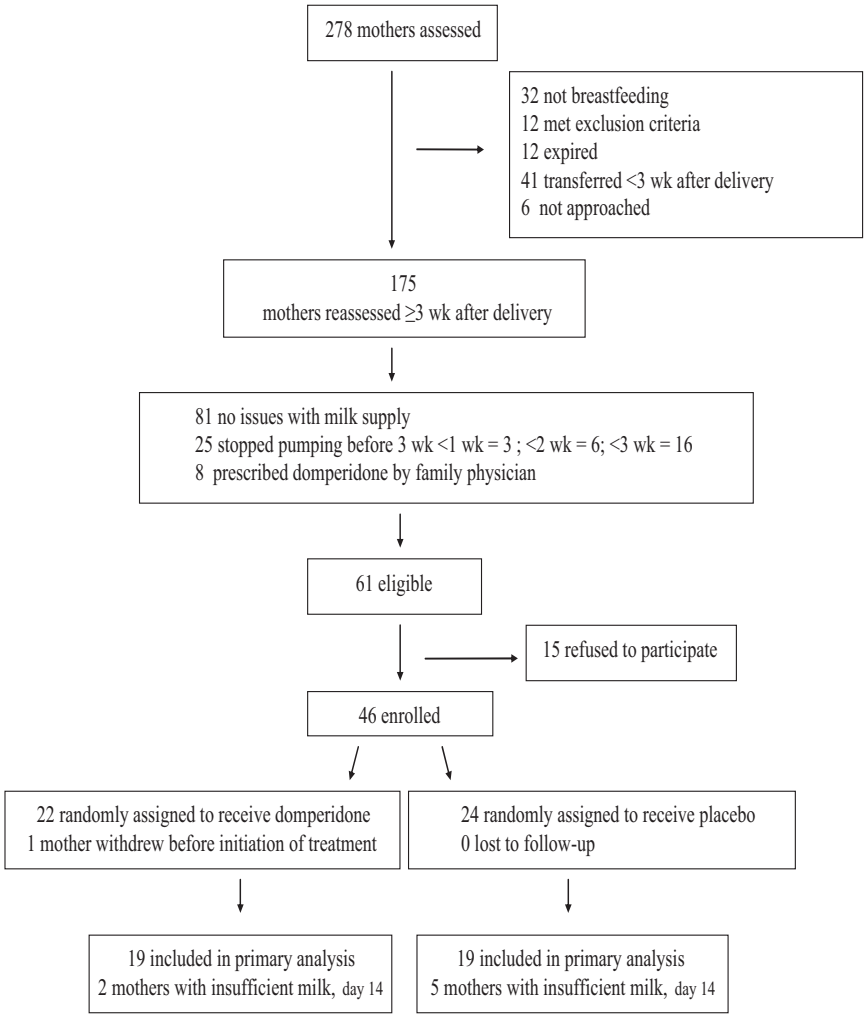

FIGURE 1
Flow diagram of subject enrollment, treatment allocation, follow-up, and inclusion in analysis.

TABLE 1 Comparison of Maternal and Infant Characteristics Between Domperidone and Placebo Groups at Randomization

Characteristic	Domperidone ($N = 22$)	Placebo ($N = 24$)	*P*
Maternal			
Mean age, y	29.1	26.3	.09
Nulliparous, *n* (%)	17 (77.2)	15 (62.5)	.44
Previous breastfeeding experience, *n* (%)[a]	4 (80.0)	7 (77.8)	.56
Education (some college or university), *n* (%)	17 (77.3)	13 (56.5)	.21
Pregnancy-induced hypertension, *n* (%)	6 (27.3)	2 (8.3)	.13
Cesarean delivery, *n* (%)	10 (45.5)	12 (50.0)	.78
Clinical chorioamnionitis, *n* (%)	9 (45.0)	11 (52.4)	.55
Infant			
Gestational age, mean (SD), wk	27.8 (1.6)	26.8 (1.9)	.06
Gestational age < 28 wk, *n* (%)	8 (36.4)	16 (66.7)	.08
Birth weight, mean (SD), g	1180.3 (408)	967.4 (307)	.05
Birth weight < 1000 g, *n* (%)	9 (40.9)	14 (58.3)	.38
Gender, male, *n* (%)	11 (50)	15 (62.5)	.55
Apgar score at 5 min, mean (SD)	7.2 (1.6)	7.1 (1.4)	.82
Apgar score at 5 min <7, *n* (%)	5 (22.7)	7 (29.2)	.74
Multiple births, *n* (%)	8 (36.4)	4 (16.7)	.24
Infant age at randomization < 4 wk, *n* (%)	17 (77.3)	18 (75.0)	.99

[a] Previous breastfeeding experience among women with a previous child.

was adjusted for these differences (see below).

One woman in the domperidone group withdrew from the study before treatment initiation. In a small fraction of the women (7 of 46), we were not able to determine macronutrient concentrations on day 14 because of insufficient milk production (volume required 30 mL). Five these of these 7 women were receiving placebos and the failure to produce sufficient milk was not unexpected. Micronutrients concentrations were estimated for these women, however, because these analyses required much smaller amounts of breast milk (1 mL volume).

Breast Milk Volumes

Mean breast milk volume on day 0 was 184 mL in the domperidone group and 218 mL in the placebo group ($P = .56$). On day 14, mean breast milk volumes were 380 mL in the domperidone group and 250 mL in the placebo group. The mean within-subject increase was 267% in the domperidone group and 19% in the placebo group ($P = .005$). Within-subject breast milk volume increased steadily from a 60% increase by day 2 to a 267% increase by day 14 in the domperidone group, compared with a fairly consistent 15% to 20% overall increase in the placebo group (Fig 2). Breast milk volume increased in all but 2 women in the domperidone group within 48 hours of treatment initiation. The mean increase in breast milk volume in the domperidone group was 106% ([380 − 184] × 100/184) and in the placebo group it was 15% ([250 − 218] × 100/218).

Prolactin Concentration

Mean prolactin concentration on day 0 was 72.1 μg/L (SD = 129.0) in the domperidone group and 50.0 μg/L (SD = 41.7) in the placebo group (Table 2). Mean within-subject serum prolactin

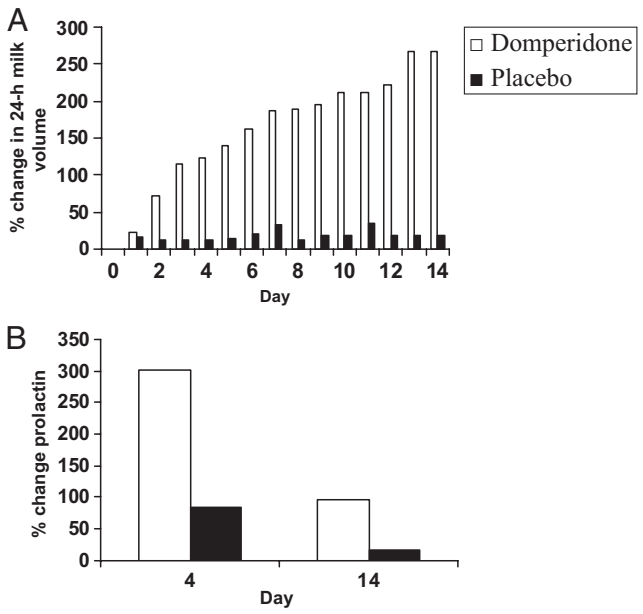

FIGURE 2
Mean within-subject percent change in 24-hour breast milk volume in the domperidone and placebo groups from day 0 to day 14 after initiation of treatment (A) and in serum prolactin concentration in the domperidone and placebo groups between days 0 and 4 and between days 0 and 14 (B).

in the domperidone group increased by 302% by day 4 compared with an 85% increase in the placebo group ($P = .03$). There was a 97% increase in mean within-subject serum prolactin by day 14 in the domperidone group compared with a 17% increase in the placebo group ($P = .07$; Fig 2). Exclusion of 1 subject in the domperidone group (who had an aberrant prolactin value on day 0 of 604 μg/L) changed the mean within-subject prolactin change between days 0 and 14 to a 107% increase (versus a 17% increase in the placebo group; $P = .04$).

Nutrient Composition

Mean breast milk protein concentration declined from 1.65 g/100 g on day 0 in the domperidone group to 1.45 g/100 g on day 14, whereas protein concentration in the placebo group increased from 1.56 g/100 g to 1.67 g/100 g (Table 2). Protein concentration on days 0, 4, 7, and 14 are shown in Fig 3.

The mean within-subject change in protein concentration was not significant between the 2 groups (−9.6% in the domperidone group versus 3.6% in the placebo group; $P = .16$). Adjustment for differences in baseline characteristics did not change these findings. Multiple linear regression adjustment for birth weight and gestational age resulted in a P value of .13 for the difference in the mean within-subject change in protein concentration between the domperidone and placebo groups. Additional adjustment for maternal age, pregnancy induced hypertension, and multiple births yielded a P value of .33 for the same difference. Additional analysis of the within-subject changes by using medians rather than the mean values showed no difference between the 2 approaches.

Fat concentration remained constant from day 0 to day 14 in both groups (3.88–3.86 g/100 g in the domperidone group; 4.15–4.05 g/100 g in the placebo group). The mean within-subject change from day 0 to day 14 was not significantly different between the 2 groups (2.0% vs −0.78; $P = .73$). Energy content was not affected by domperidone. However, the within-subject mean percent change in the carbohydrate content of breast milk between days 0 and 14 was higher in the dom-

TABLE 2 Breast Milk Volume and Composition on Days 0 and 14 in the Domperidone and Placebo Groups and Mean Within-Subject Change Between Days 0 and 14

Parameter	Domperidone ($N = 21$)[a]		Within-Subject Change, %	Placebo ($N = 24$)[a]		Within-Subject Change, %	P[b]
	Day 0	Day 14		Day 0	Day 14		
24-h milk volume, mean (SD), mL	184.4 (167.0)	380.2 (201.6)	266.8	217.7 (154.5)	250.8 (171.6)	18.5	.005
Prolactin, mean (SD), μg/L	72.1 (129.0)	81.3 (70.8)	96.8	50.0 (41.7)	36.0 (26.2)	16.7	.07
Protein, mean (SD), g/100 g	1.65 (0.47)	1.45 (0.24)	−9.6	1.56 (0.31)	1.67 (1.1)	3.6	.16
Energy, mean (SD), cal/100 g	69.7 (7.8)	69.4 (7.9)	0.5	67.9 (7.7)	70.1 (9.0)	−2.2	.53
Fat, mean (SD), g/100 g	3.88 (0.73)	3.86 (0.86)	2.0	4.15 (0.88)	4.05 (1.0)	−0.78	.73
Carbohydrate, mean (SD), g/100 g	7.04 (0.47)	7.21 (0.29)	2.7	7.18 (0.32)	6.98 (0.69)	−2.7	.05
Sodium, mean (SD), mmol/L	20.3 (21.5)	18.4 (21.7)	−7.6	15.8 (16.3)	17.2 (19.4)	23.0	.13
Calcium, mean (SD), mmol/L	4.83 (1.74)	6.85 (2.6)	61.8	5.50 (1.55)	5.21 (1.8)	−4.4	.02
Phosphate, mean (SD), mmol/L	2.09 (0.43)	2.05 (0.31)	0.12	2.13 (0.54)	1.94 (0.42)	−7.3	.11

[a] Macronutrient levels on day 14 could not be determined for 2 women in the domperidone group and 5 women in the placebo group because of insufficient milk production.
[b] P values express the statistical significance of the difference between the mean within-subject change between day 0 and day 14 in the domperidone group and the mean within-subject change between days 0 and 14 in the placebo group. Note that mean within-subject change differs from a change in the mean of the group (see the main text).

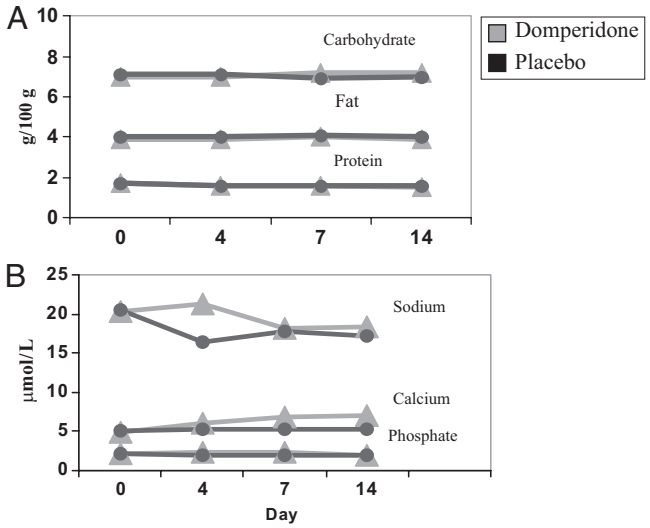

FIGURE 3
Mean concentrations of protein, fat, and carbohydrate in breast milk (A), and of sodium, calcium, and phosphate (B) in the domperidone and placebo groups on days 0, 4, 7, and 14.

peridone group (2.7% increase versus −2.7% decrease), and the difference was nominally significant ($P = .05$).

The within-subject change in sodium and phosphate content of breast milk was not different between groups (Table 2). Within-subject change in calcium content was significantly different in the 2 groups, however, with calcium concentration increasing by 61.8% in the domperidone group and decreasing by 4.4% in the placebo group ($P = .02$).

Breastfeeding Rates, Adherence to Treatment, and Adverse Events

There were no significant differences between the 2 groups with respect to mean pumping frequency (5.6 times per day in the domperidone group versus 5.3 times per day in the placebo group). At 2 weeks after the end of the study period, the breastfeeding rate in the domperidone group was 86.4% (19 of 22), whereas in the placebo group it was 62.5% (15 of 24) ($P = .13$). At discharge, the breastfeeding rates were 54.6% (12 of 22) in domperidone group and 52.2% (12 of 23) in the placebo group. These rates may have been influenced by domperidone use after study completion (63.6% [14 of 22] in the domperidone group and 41.7% [10 of 24] in the placebo group).

One subject on domperidone returned 35 of 45 pills dispensed. No significant adverse events were observed in the 2 groups among mothers and infants. One mother in the placebo group reported mild abdominal cramps.

DISCUSSION

Our study showed that domperidone increased serum prolactin levels and breast milk volume substantially, and these findings were consistent with the known effect of domperidone as a galactagogue. However, the changes in breast milk volume occurred without concomitant changes in breast milk protein and no adverse effects were observed among mothers and infants. Despite the smaller-than-planned size of our study, the findings of our study suggest that domperidone is an efficacious galactagogue that increases breast milk volume without altering nutrient content.

Protein concentrations at baseline in the domperidone and placebo groups (1.65 g/100 g and 1.56 g/100 g, respectively) were similar to previously reported values for preterm milk at 3 to 4 weeks after delivery.[36] The small decline in protein level between days 0 and 14 in the domperidone group did not exceed the expected rate of decline,[35] whereas the small increase in protein concentration seen in the placebo group was not consistent with the expected decline in protein concentration over time.[37] Nevertheless, the change in protein concentration in the domperidone group was not significantly different from the change in protein concentration in the placebo group.

The increase in the volume of breast milk among mothers in our trial exceeded that reported from a previous study.[19] We observed a 267% increase compared with a 45% increase reported in a similar population of mothers who had received the same dose of domperidone.[19] The differential increase in breast milk volume may reflect the higher baseline milk volumes and higher prolactin levels of mothers in our study. Also, mothers in our study received domperidone for 14 days (vs 7 days),[19] and the majority of mothers in our study initiated treatment between 21 and 28 days after delivery (compared with an average of 32–33 days).[19] Finally, for methodologic reasons we chose to calculate mean within-subject change within groups, whereas the authors of the previous study estimated the change in group means.

None of the mothers in the domperidone group reported any adverse effects. None of the infants were reported to have any adverse events related to the gastrointestinal tract, central nervous system, integument structures, or cardiovascular system. These findings are consistent with previous studies that used the same dose of domperidone.[19,38]

The lack of differences between baseline and day 14 solute characteristics

between groups, (especially with regard to sodium) suggests that mammary tight junction closure at the cellular level and epithelial integrity were preserved in domperidone and placebo groups despite the significant postnatal lowering of milk volume. The small rise in carbohydrate concentration may be attributed to the higher volume of breast milk produced by the mothers in the domperidone group.[35] Our study also showed an increase in calcium concentration in the breast milk of subjects receiving domperidone. Although the full significance of this increase in calcium concentration is uncertain, the authors of previous studies suggested that effects on bone mineral density are temporary.[39,40]

Although we planned to study 44 women, we recruited 46 subjects. Of these, 1 withdrew from the study and 7 were not producing sufficient breast milk for a day 14 estimation of macronutrient concentrations. This small decrease in study size represents a potential weakness of our study. Although our study adds to the evidence regarding the efficacy of domperidone as a galactagogue for mothers of preterm infants, additional studies are required to confirm our findings.

CONCLUSIONS

Our study shows that domperidone, at a dose of 10 mg 3 times daily for 2 weeks, effectively increases breast milk volume without alteration in the nutrient composition of very preterm mother's milk. The increase in calcium concentration in breast milk after domperidone use requires additional study because it relates to both maternal and infant effects.

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