

# Effect of domperidone on milk production in mothers of premature newborns: a randomized, double-blind, placebo-controlled trial

Orlando P. da Silva,\* David C. Knoppert,† Michelle M. Angelini,‡ Penelope A. Forret‡

## Abstract

**Background:** Varying degrees of success have been reported with strategies to increase milk production when lactation is failing. The objective of this study was to investigate the efficacy of domperidone in augmenting milk production in mothers of premature newborns.

**Methods:** Twenty patients were randomly assigned to receive either domperidone or placebo for 7 days. Milk volume was measured daily. Domperidone levels were measured in randomly selected milk and serum samples on day 5 of the study. Serum prolactin levels were measured before the start of the study, on day 5 and on day 10 (3 days after the last dose of the study medication).

**Results:** Data from 16 patients were available for analysis (7 in the domperidone group and 9 in the placebo group). When compared with baseline values, the mean increase in the volume of milk production from day 2 to 7 was 49.5 (standard deviation [SD] 29.4) mL in the domperidone group and 8.0 (SD 39.5) mL in the placebo group ( $p < 0.05$ ); proportionally this represented an increase of 44.5% and 16.6% respectively. The serum prolactin levels were similar in the 2 groups at baseline; by day 5 they were significantly higher in the domperidone group than in the placebo group, returning to baseline levels in both groups 3 days after the last dose of the study medication. Very small amounts of domperidone were detected in the breast milk samples.

**Interpretation:** In the short term domperidone increases milk production in women with low milk supply and is detected at low levels in breast milk.

Breastfeeding is recommended as the optimal form of nutrition for term and premature infants.<sup>1,2</sup> There are several advantages to breastfeeding, including the psychological benefits of maternal–infant bonding, gastrointestinal trophic aspects and anti-infective benefits for the infant.<sup>1–10</sup> In addition, there is some evidence that the use of human milk may be associated with long-term benefits for intellectual development even when used for a short period.<sup>11–13</sup> When direct breastfeeding is not possible, the use of expressed mother's milk, fortified when necessary, is recommended to achieve the high nutrient demands of the very-low-birth-weight infant.<sup>1–5</sup> However, mothers who wish to express milk for their hospitalized premature newborns are faced with numerous stressful situations. The often unstable clinical condition of the infant combined with concerns about prognosis and survival, and the distance from home, frequently have a detrimental effect on milk supply.

Varying degrees of success have been reported with strategies to increase milk production when lactation is failing, including support, relaxation techniques, mechanical expression and drug therapy.<sup>14–17</sup> Of all the pharmacological interventions to augment lactation, metoclopramide, a central dopamine antagonist, has been the most widely studied.<sup>15,18–21</sup> However, it crosses the blood–brain barrier, is secreted in significant amounts in breast milk<sup>17,22–24</sup> and has been reported to affect dopamine-mediated responses in offspring of nursing rats.<sup>25</sup>

Domperidone is a peripheral dopamine antagonist that is indicated for use as an

## Research

## Recherche

From the Departments of \*Pediatrics, †Pharmacy and ‡Nursing, University of Western Ontario and St. Joseph's Health Care London, London, Ont.

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upper gastrointestinal motility modifier.<sup>26</sup> Unlike metoclopramide, it does not readily cross the blood–brain barrier.<sup>26–28</sup> Preliminary data suggest that domperidone may be useful in augmenting milk production in women with insufficient lactation.<sup>29,30</sup> However, these studies had several methodological shortcomings, including inappropriate control groups and no information on the blinding of subjects or the method of randomization, and in both studies the infants were weighed before and after breastfeeding, an unreliable method at best.

We conducted a randomized, double-blind, placebo-controlled trial to assess the efficacy of domperidone in augmenting lactation in mothers of premature infants. Secondary objectives included the determination of serum prolactin levels in response to orally administered domperidone and of domperidone levels in serum and breast milk.

### Methods

The study design was approved by the University of Western Ontario Ethics Committee on Research Involving Human Subjects and the Hospital Clinical Research and Pharmacy and Therapeutics Committees.

The study group included puerperal subjects who had their infants admitted to the neonatal intensive care unit at St. Joseph’s Health Care London, in London, Ont. All mothers were mechanically expressing breast milk to be fed to their infants through a nasogastric tube. The women were assessed by our team of lactation consultants and extensively counselled before entering the study. If the milk production remained low (did not meet the infant’s daily oral feeding requirements) mothers were informed about our study. They were eligible to participate if they were using an electric breast pump with a double collection kit, were not receiving any medication known to affect serum prolactin levels and did not have a chronic or debilitating illness.

After informed consent was obtained, mothers were randomly assigned to receive either domperidone (10 mg orally 3 times daily) or placebo for 7 days. Domperidone tablets were crushed and mixed with lactose. The resulting powder was placed in clear capsules, as was plain lactose powder, which acted as the placebo.

Breast milk was collected using the Lactina double breast pump (Medela Canada, Mississauga, Ont.). Each subject received an ample supply of collection bottles. These one-time use sterile containers accurately measure the volume of milk to the millilitre. The women were instructed to use a new container for each pumping and not to add milk together from 2 different pumpings. They were given recording sheets and adhesive labels to record the amount of milk collected, the date and the time. Milk volume was measured daily. A small amount of milk was retained from all patients on study day 5 for the measurement of domperidone concentrations. The mothers were instructed to record any side effects during treatment, particularly dry mouth, headache, insomnia, abdominal cramps, diarrhea, nausea and urinary retention. The record was reviewed with each woman on day 5 and on day 10 (3 days after the last dose of the study medication), at the time of the visit for blood sampling.

Three blood samples were obtained from each patient to determine serum domperidone and prolactin concentrations before the initial dose, on day 5 and on day 10. All serum and milk samples were kept frozen at –20°C for later analysis. Serum prolactin concentrations were determined using the IMx prolactin assay

(Abbott Laboratories, Abbott Park, Ill.), a microparticle enzyme immunoassay. The analyzer used was an Abbott IMx Automated Immunoassay Analyzer. Domperidone concentrations were determined by means of isocratic reversed-phase high-performance liquid chromatography with mass selective detection.<sup>31</sup>

We calculated that 20 subjects would need to be enrolled to demonstrate an increase of at least 25% in milk production (considered clinically significant) from baseline in the study group compared with the placebo group at a power of 80% and an  $\alpha$  level of 0.05. Categorical data between the 2 groups were compared with the  $\chi^2$  test, and continuous data were compared with Student’s *t*-test. The mean increase in the volume of milk from baseline in the 2 groups was compared with the Wilcoxon rank sum test. Simple randomization was achieved using a random numbers table, and patient allocation was carried out in the hospital pharmacy using opaque sealed envelopes. Neither the patients nor the practitioners knew the treatment assignment.

### Results

Of the 23 eligible women 20 agreed to participate in the study (Fig. 1). Four of the 20 women were excluded from the final analysis: no milk records were returned in 3 cases, and in 1 case the infant died of neonatal complications shortly after enrolment. The mean maternal age, gestational age at delivery, post-delivery day at study entry, parity, smoking habits, reasons for preterm delivery and previous breastfeeding experience were similar in the 2 groups (Table 1).

The baseline milk production (the volume produced in the 24 hours before the start of the study medication) was

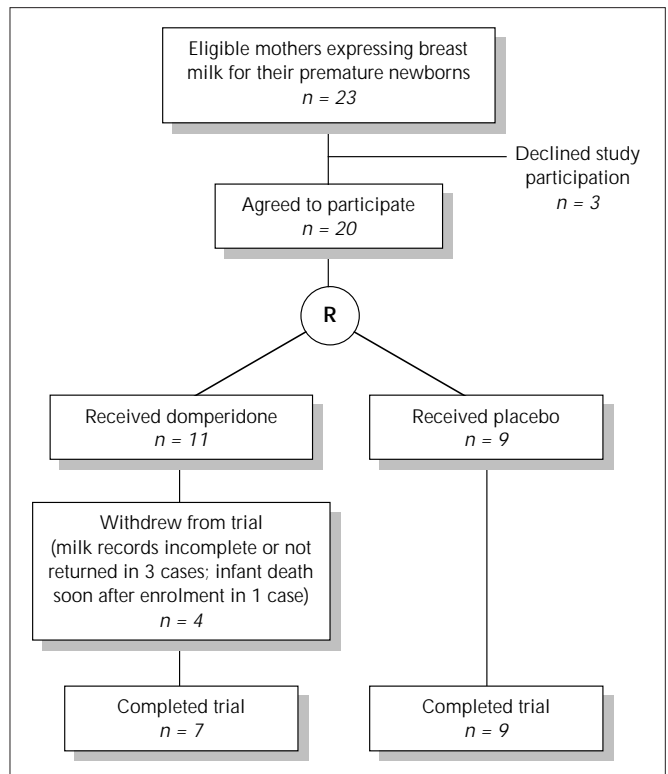


Fig. 1: Profile of trial. R = randomization.

not available for 4 of the remaining 16 subjects (3 in the placebo group and 1 in the domperidone group); the volume of milk produced in the 24 hours following enrolment was taken as the baseline in these cases. The mean volume of milk at baseline was 112.8 (standard deviation [SD] 128.7) mL in the domperidone group and 48.2 (SD 63.3) mL in the placebo group. The mean daily volume of milk collected during study days 2 to 7 was 162.2 (SD 127.5) mL in the domperidone group and 56.1 (SD 48.0) mL in the placebo group. Compared with baseline values the mean increase was significantly greater in the domperidone group than in the placebo group (49.5 [SD 29.4] mL versus 8.0 [SD 39.5] mL respectively,  $p < 0.05$ ). Proportionally this represented an increase from baseline of 44.5% and 16.6% respectively. The daily milk records for each patient are shown in Table 2.

At baseline the mean serum prolactin levels were similar in the domperidone and placebo groups (12.9 [SD 7.7]  $\mu\text{g/L}$  and 15.6 [SD 17]  $\mu\text{g/L}$  respectively,  $p = 0.70$ ). By day 5 there was a significantly greater increase in the serum prolactin levels in the domperidone group than in the placebo group (119.3 [SD 97.3]  $\mu\text{g/L}$  v. 18.1 [SD 14.7]  $\mu\text{g/L}$ ,  $p = 0.008$ ). These values returned to baseline levels by day 10 (3 days after the last dose of the study medication): 12.1 (SD 5.1)  $\mu\text{g/L}$  in the domperidone group and 16.5 (SD 5.2)  $\mu\text{g/L}$  in the control group ( $p = 0.11$ ).

On day 5, subjects in the treatment group had a mean domperidone concentration (as measured in randomly selected serum and milk samples) of 6.6 (SD 5.7) ng/mL in serum ( $n = 6$ ) and 1.2 (SD 0.6) ng/mL in breast milk ( $n = 6$ ). The serum and milk domperidone levels in the placebo group were below the limit of detection of the assay used.

Compliance was monitored by capsule count. All subjects complied with the assigned treatment group. In one instance a subject assigned to the domperidone group stopped taking the drug on day 4 of the study because she started to breastfeed her infant successfully. One woman in

the placebo group failed to return milk records during the latter part of the study period. Data on these patients were included in the final analysis. No side effects were reported during the study. No obvious adverse effects were identified after reviewing the infants' records. The proportion of infants discharged home who were breastfeeding did not differ between the 2 groups.

## Interpretation

There is a paucity of information in the literature regarding the role of domperidone as a galactagogue. Given the importance of breast milk in the feeding of newborns, every effort should be made to enhance breast milk production in lactating mothers of infants admitted to a neonatal intensive care unit. These mothers are usually faced with many barriers to initiating and sustaining lactation given the baby's critical clinical condition and the limitations of breast pumping in the long term. Our study has shown that domperidone is a safe and effective medication in the short term.

Because the infants in our study were not yet nursing we could accurately measure the milk volume collected on a daily basis. Women in the domperidone group experienced a steady increase in milk volume, starting 48 hours after initiation of the medication and continuing gradually up to the last day of treatment. We could not correlate this steady increase in milk volume with the raise in hormone levels, because the serum prolactin level was measured only 3 times during the study period.

How domperidone increases milk production is not well understood. It is hypothesized that the drug stimulates prolactin secretion.<sup>24,29</sup> Our results support this hypothesis: we found a significantly greater rise in the serum prolactin levels in the domperidone group than in the placebo group.

Very small concentrations of domperidone were found in the breast milk samples randomly selected on day 5; this finding is in keeping with the findings of other investiga-

**Table 1: Characteristics of mothers expressing low volumes of breast milk for their premature newborns who were randomly assigned to receive either domperidone or placebo**

Characteristic	Received domperidone <i>n</i> = 7	Received placebo <i>n</i> = 9	<i>p</i> value
Mean maternal age (and SD), yr	28.2 (5.0)	27.9 (6.6)	NS
Mean gestational age (and SD), wk	29.1 (2.0)	29.1 (3.7)	NS
Mean no. of days between delivery and study entry (and SD)	31.9 (10.5)	33.1 (22.9)	NS
First pregnancy, no. of women	3	3	NS
No. who breastfed previously	1	3	NS
No. who smoked	0	1	NS
Reason for preterm delivery, no. of women			
Spontaneous labour	5	6	NS
Pregnancy-induced hypertension	2	3	NS

Note: SD = standard deviation.

tors.<sup>23,24</sup> The milk:serum ratio in our study (0.4) is within the range reported for a small number of women in an earlier study.<sup>24</sup> This relatively low value is likely related to domperidone's high protein binding (greater than 90%)<sup>32</sup> and to its relatively high molecular weight. The amount of domperidone that would be ingested by the infant would be extremely small (less than 0.2 µg/kg daily, assuming a daily milk intake of 150 mL/kg and a milk domperidone concentration of 1.2 ng/mL found in this study). This amount is much lower than the level of metoclopramide (approximately 125 ng/mL) that has been measured in the breast milk of nursing mothers treated with this drug.<sup>23,24</sup> Upon reviewing the infants' charts, we found no reported side effects attributable to domperidone.

Milk production at baseline was higher in the domperidone group than in the placebo group. One possible explanation could be that 3 patients in the domperidone group had delivered multiples (2 sets of triplets and 1 set of twins), as compared with only one set of multiples in the placebo group. Proportionally these patients did not experience a greater response to domperidone than the ones with a lower milk output. The relatively long delay between delivery and study entry is explained by the fact that all women failing lactation in our centre received extensive teaching by our team of lactation consultants. The majority of women responded favourably with improvement in milk production.

The women who continued to have problems with lactation after the teaching were eligible to enter the study.

We did not evaluate long-term milk production because most of the women initiated some level of breastfeeding soon after the end of the 7-day trial, and it was not practical to measure milk volume beyond the study period. Therefore we were unable to determine whether the increase in milk volume with domperidone was sustained.

Many questions need to be answered before domperidone can be routinely recommended to increase lactation. In particular, it is not known whether the short-term benefit of domperidone will be sustained. Also, the long-term effects of this drug on the infant, if any, need to be determined. A large multicentre trial should be conducted to address these questions.

*Competing interests:* None declared.

*Contributors:* Orlando da Silva co-wrote the protocol, coordinated the study, managed the data, and contributed to and coordinated the writing and revision of the manuscript. David Knoppert co-wrote the protocol, conducted the randomization, dispensed the study drug and contributed to the writing and revision of the manuscript. Michelle Angelini and Penelope Forret contributed to the writing of the protocol, recruited patients, counselled mothers with breast-feeding techniques, took blood samples for analysis, collected the clinical data and contributed to the writing of the manuscript.

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**Table 2: Daily volumes of breast milk recorded by subjects in the domperidone and placebo groups**

Patient	Study day: milk volume, mL						
	Baseline*	2	3	4	5	6	7
<b>Domperidone</b>							
1	13†	3	49	66	51	68	45
2	262	286	291	342	323	337	346
3	6	21	19	35	39	45	45
4	17	49	81	121	146	170	190
5	120	135	167	132	–	–	–
6	51	69	95	96	125	126	125
7	320	350	356	385	378	323	350
Mean volume	112.8	130.4	151.1	168.1	177.0	178.2	183.5
<b>Placebo</b>							
1	201†	152	180	102	133	80	110
2	12†	14	15	16	12	14	14
3	32†	36	36	32	36	40	40
4	14	37	62	55	42	57	58
5	11	28	18	8	4	0	0
6	50	92	82	120	121	150	180
7	89	102	94	111	95	101	107
8	23	21	22	22	–	–	–
9	< 1	10	20	25	27	15	19
Mean volume	48.2	54.7	58.8	54.6	58.8	57.1	66.1

\*Defined as the volume of milk produced during the 24 hours before the start of the study medication.

†Baseline volume was unavailable; instead, volume produced within the 24 hours following enrolment was considered as the baseline.



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Reprint requests to: Dr. Orlando P. da Silva, Department of Pediatrics, St. Joseph's Health Care London, 268 Grosvenor St., London ON N6A 4V2; fax 519 646-6123; odasilva@julian.uwo.ca

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