


# Use of Domperidone as a Galactagogue Drug: A Systematic Review of the Benefit-Risk Ratio

Journal of Human Lactation  
2015, Vol. 31(1) 57–63  
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DOI: 10.1177/0890334414561265  
jhl.sagepub.com  


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## Abstract

Breastfeeding is the optimal method for feeding a newborn. However, some mothers may have difficulties lactating. Domperidone is widely used as a galactagogue but to the best of our knowledge has not been approved by any health authority. The objective of this review was to assess the benefit-risk ratio of domperidone for stimulating lactation. The benefit-risk ratio of domperidone as a galactagogue was assessed following a literature search of the PubMed database up to July 2013. Four studies were selected to assess domperidone efficacy and demonstrated an increased milk production. The limited data (60 mother-baby pairs) and the moderate methodological quality of 1 study remain insufficient to conclude on domperidone efficacy. Regarding the safety of domperidone, 7 studies were selected that exposed 113 infants to domperidone through breastfeeding. No adverse effects were observed in 85 infants, and no information was provided for the remaining 28. The limited data available remain in favor of a safe domperidone profile in infants and mothers. However, in large studies focused on gastrointestinal disorders, domperidone is responsible for drug-induced long QT syndrome and sudden cardiac death. The use of domperidone as a galactagogue is worrisome as drug-induced long QT syndrome occurred mostly in women. In these circumstances, an improvement of breastfeeding practices seems to be more effective and safer than the use of an off-label domperidone treatment.

## Keywords

benefit-risk ratio, breastfeeding, domperidone

## Background

Mothers who delivered preterm infants often have difficulties producing sufficient amounts of milk.<sup>1</sup> Additionally, mothers of term infants can have, under certain circumstances, difficulties with producing enough milk for their infants (eg, maternal illness, cesarean delivery, maternal smoking, previous breast surgery, mother-infant separation, and psychosomatic disorders).<sup>2,3</sup> Women and clinicians often turn to galactagogue drugs or supplements to try and increase supply.<sup>3</sup> The use of dopamine receptor antagonists, such as metoclopramide or domperidone, is probably the most widespread pharmacological strategy.<sup>4</sup>

Domperidone is a prokinetic and antiemetic drug for the treatment of gastroparesis, nausea, and vomiting, approved worldwide with the exception of the US (mainly due to cardiotoxicity).<sup>5,6</sup> Antiemetic activity results from the association of peripheral effects on gastric motility and dopaminergic antagonism of the chemoreceptors in the trigger zone, which is outside the blood brain barrier in the area postrema.<sup>7</sup> Domperidone has a strong affinity for dopaminergic D2 receptors in the peripheral nervous system and the gastrointestinal system.<sup>7</sup> Despite its antidopaminergic effect, domperidone is rarely responsible for extrapyramidal side effects because it hardly crosses the blood brain barrier.<sup>8</sup>

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Date submitted: April 29, 2014; Date accepted: November 3, 2014.

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Domperidone is rapidly absorbed after oral intake, with a peak plasma concentration between 30 and 60 minutes. However, the oral bioavailability is low (15%) due to hepatic first pass metabolism. Food intake delays the peak plasma concentration but increases the bioavailability. Domperidone binds strongly to plasma protein (91%-93%) and is widely distributed in tissues, with the exception of the central nervous system. After oral administration, domperidone is rapidly and intensively metabolized by hydroxylation and N-dealkylation by CYP3A enzymes in the gut wall and the liver.<sup>9</sup> Two-thirds of the administered dose are eliminated in feces and the remaining third in urine, mainly as metabolites (90%). Plasma half-life after oral intake is about 7 to 9 hours and increases in cases of renal failure.<sup>8</sup>

The use of domperidone as a galactagogue was first described in 1983.<sup>10</sup> This property results from its antidopaminergic effect on D2 receptors of the lactotropic cells of the anterior pituitary gland, bearing in mind that dopamine is the main inhibitor of prolactin release.<sup>11</sup> In a randomized clinical trial, the prolactinemia of treated women ( $n = 24$ ) increased by 302% compared to 85% in control women ( $n = 21$ ) ( $P = .03$ ) after 4 days of domperidone treatment (10 mg, 3 times a day). After 14 days of domperidone treatment, the increase of the prolactinemia was only 107% in treated women compared to 17% in control women ( $P = .07$ ).<sup>12</sup> Galactorrhea following domperidone treatment remains, however, a rare adverse drug reaction (frequency:  $> 1/1000$  and  $< 1/10000$ ).<sup>8</sup>

To the best of our knowledge, the use of domperidone as a galactagogue has not been approved by any authority.<sup>13</sup> Consequently, an adequate assessment of the benefit-risk ratio of domperidone is essential before prescribing this drug for lactation failure. The objective of this systematic review of the literature was to conduct an assessment of the benefit-risk ratio of domperidone use as a galactagogue, with regards to milk production, excretion of domperidone in milk, quality of milk, and safety of the mothers and infants during domperidone treatment.

## Methods

A single author performed a literature search of the PubMed database (up to July 2013) in order to assess the benefit-risk ratio of domperidone. The search used the keywords *domperidone* associated with *lactation*, *galactagogue*, *milk*, or *breastfeeding*. The bibliographic analysis was limited to clinical trials and meta-analyses published in French or in English. Exclusion criteria were chosen as follows: nonclinical study, non-English or French publication, review, letter, case report, study protocol, guideline, different topic than lactation (eg, digestive pathology, galactorrhoea, analytical method), low quality study (eg, observational study, methodological bias).

For the assessment of domperidone efficacy and maternal safety, only the publications measuring the production of milk in lactating women and comparing a domperidone treated group to a control group were selected for the review. For the assessment of domperidone safety in infants, publications were selected if the infants were exposed to domperidone through breastfeeding.

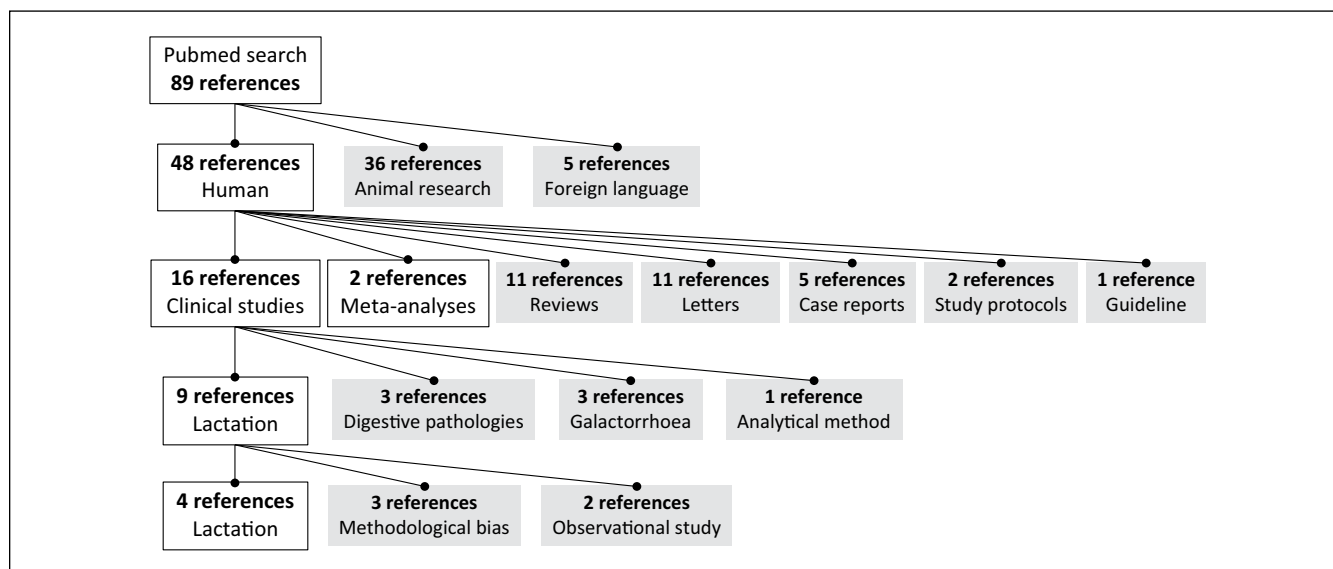
## Results

### Bibliographic Results

The literature search collected 89 references, and the selection of the references for the review is presented in the Figure 1. Two meta-analyses assessing domperidone efficacy as a galactagogue have been identified and selected.<sup>14,15</sup> Seven clinical studies focusing on domperidone and lactation have been identified.<sup>12,13,16-20</sup> Among the remaining 7 publications, 4 studies fulfilled the inclusion criteria of domperidone efficacy,<sup>12,18-20</sup> and 3 studies<sup>13,16,17</sup> were excluded due to methodological bias (absence of control groups or irrelevant comparator). The domperidone safety in infants was assessed from the 7 publications corresponding to infants exposed to domperidone through breastfeeding.<sup>12,13,16-20</sup>

### Domperidone Efficacy as a Galactagogue

All 4 studies selected from the literature search were controlled double-blind studies,<sup>12,18-20</sup> and 3 studies<sup>12,18,20</sup> were randomized (Table 1). Women were included due to an inadequate postpartum milk production<sup>12,18,19</sup> or after a cesarean birth.<sup>20</sup> All definitions of lactation insufficiency were accepted, the most frequent definition being a milk production insufficient for the daily needs of the infant. All the mothers who delivered vaginally were included a few weeks after the delivery, leaving a sufficient period necessary for the initiation of lactation, with lactation support if required. However, only 1 study<sup>19</sup> mentioned that advice on improving lactation had been given before inclusion into the trial. For the mothers who delivered by cesarean section, the domperidone treatment was initiated as soon as they were able to take liquid beverages, namely, 24 hours after the delivery. In these 3 studies, the doses of domperidone were approximately 30 to 40 mg/day (10 mg, 3-4 times *per os*). A double-blind procedure was used for the administration of the drug. Treatment duration was between 7 and 14 days. In the study by Petraglia et al,<sup>19</sup> the mothers breastfed their infants born at full term. The quantity of milk produced was estimated every day by weighing the infants before and after breastfeeding.<sup>19</sup> In the others 3 studies, the mothers who gave birth prematurely<sup>12,18</sup> or by cesarean section at term<sup>20</sup> fed their babies with milk collected using a pump. In these studies, the quantities of produced milk were assessed after collection.<sup>12,18,20</sup>

**Figure 1.** Flow Chart of the Literature Search in the PubMed Database (up to July 2013) for Domperidone Efficacy.

The search used the keywords *domperidone* associated with *lactation*, *galactagogue*, *milk*, or *breastfeeding*. The references in grey have been excluded from the review according to inclusion/exclusion criteria.

The methodological quality of the studies by Campbell-Yeo et al,<sup>12</sup> Da Silva et al,<sup>18</sup> and Petraglia et al<sup>19</sup> were assessed by meta-analysis.<sup>15</sup> For the studies by Campbell-Yeo et al<sup>12</sup> and Da Silva et al,<sup>8</sup> the randomization, blinding procedures, and results were judged satisfactory. However, in the study by Da Silva et al,<sup>18</sup> data were missing for 3 of the 11 participants (domperidone group). Despite this missing data, the 2 studies were considered of good quality and without serious bias. Conversely, the study by Petraglia et al<sup>19</sup> did not give sufficient information about the blinding procedure. This study is defined as a double-blind trial. However, neither was it stated if the appearance and taste of the active and placebo forms were similar nor if the initially randomized mothers participated until the end of the trial. Considering these methodological issues, this study was judged to be of moderate quality.

Da Silva et al<sup>18</sup> found that between the first and the seventh day of treatment, the volume of milk produced increased by  $49.5 \pm 29.4$  ml/day (44.5%) in the domperidone group compared to  $8.0 \pm 39.5$  ml/day (16.6%) in the control group ( $P < .05$ ). Petraglia et al<sup>19</sup> showed that after 10 days of treatment, the daily milk production increased for the domperidone treated mothers, with a mean increase of 326 ml/day compared to 63 ml/day in the control group ( $P < .01$ ). Campbell-Yeo et al<sup>12</sup> demonstrated an increase in daily milk production of 267% after 14 days of domperidone treatment compared to 18.5% in the control group ( $P = .005$ ). Finally, Jantarasengaram et al<sup>20</sup> showed that the volume of collected milk was approximately  $191.0 \pm 136.1$  ml/day after 4 days of domperidone treatment compared to  $91.4 \pm 60.3$  ml/day in the control group ( $P = .003$ ). The mean volume of milk produced before the beginning of treatment in the domperidone

and control group was  $3.9 \pm 4.6$  ml/day and  $3.4 \pm 9.3$  ml/day, respectively.<sup>20</sup>

The prolactin concentrations in the blood of patients have been assessed in 3 of these studies, and they report a significant increase of prolactin concentrations between 300% and 800% compared to baseline values.<sup>12,18,19</sup> After 5 days of domperidone treatment (10 mg 3 times daily), serum prolactin levels were about  $119.3 \pm 97.3$   $\mu$ g/L in the domperidone group compared to  $18.1 \pm 14.7$   $\mu$ g/L in the placebo group ( $P = .008$ ).<sup>18</sup>

In conclusion, these studies demonstrated an increased milk production after domperidone treatment in mothers at risk of lactation failure, as well as in mothers after a cesarean delivery at full term. The recent meta-analysis by Donovan and Buchanan demonstrated a modest increase in expressed breast milk of 99.49 mL/day (95% confidence interval,  $-1.94$  to  $200.92$ ); random-effects,  $T^2$  3511.62,  $I^2$  63%).<sup>14</sup> The meta-analysis by Osadchy et al<sup>15</sup> was more encouraging and reported a significant increase in daily milk production of 74.72% (95% confidence interval, 54.57-94.86). However, considering the limited data (only 60 mother-baby pairs treated with domperidone in the 4 selected studies) and the moderate methodological quality of the Petraglia et al<sup>19</sup> study, scientific proofs remain insufficient to conclude on the clinical efficacy of domperidone as a galactagogue.

A multicenter, double-blind, and randomized clinical trial to assess domperidone efficacy in breastfeeding deficiency, with a planned inclusion of 560 mothers of preterm neonates and funded by the Canadian Institutes of Health Research, is currently ongoing.<sup>21</sup> The results are expected in 2016 and should give sufficient information on the galactagogue properties of domperidone and its efficacy and safety.

Table 1. Main Features of the 4 Included Studies.

Study	Study Location	Participants Domperidone/ Control, n; Type of Delivery; Term	Study Design	Domperidone Dose	Milk Volume, mL/day, mean ± SD; Day of Measure	Prolactin Values, µg/L, mean ± SD; Day of Measure	Maternal Safety	Infant Safety
Jantarsaengaram et al, 2012 <sup>20</sup>	Obstetrics and gynecology department, Thailand	22/23; 100% cesarean delivery; term infants	Double-blind randomized controlled trial	10 mg orally 4 times daily for 4 days	D: 191.3 ± 136.1; C: 91.4 ± 60.3; day 4	No information	D: Dry mouth (7 mothers) C: No adverse effect	No information
Campbell-Yeo et al, 2010 <sup>12</sup>	Neonatal intensive care unit, Canada	22/24; D: 45.5% cesarean delivery, C: 50% cesarean delivery; preterm infants < 31 weeks gestation	Double-blind randomized controlled trial	10 mg orally 3 times daily for 2 weeks	D: 380.2 ± 201.6; C: 250.8 ± 171.6; day 14	D: 81.3 ± 70.8; C: 36.0 ± 26.2; day 14	D: No adverse effect C: Mild abdominal cramp (1 mother)	No adverse effect
Petraglia et al, 1985 <sup>19</sup>	Obstetrics and gynecology department, Italy	9/8; vaginal delivery; term infants	Double-blind controlled trial	10 mg orally 3 times daily for 10 days	D: 673 ± 44; C: 398 ± 45; day 10	D: 146.9 ± 14.8; C: 65.4 ± 13.6; day 5	No adverse effect	No adverse effect
Da Silva et al, 2001 <sup>18</sup>	Neonatal intensive care unit, Canada	7/9; unknown; preterm infants	Double-blind randomized controlled trial	10 mg orally 3 times daily for 7 days	D: 183.5 ± 138.5; C: 66.0 ± 61.7; day 7	D: 119.3 ± 97.3; C: 18.1 ± 14.7; day 5	No adverse effect	No adverse effect

Abbreviations: C, control; D, domperidone.

### **Domperidone Doses and Treatment Duration for Stimulating Lactation**

In the summary of product characteristics (regulatory drug information for professionals), the approved domperidone dose for the treatment of gastroparesis, nausea, and vomiting is 10 to 20 mg 3 to 4 times daily, with a maximal daily dose of 80 mg.<sup>8</sup> However, as a galactagogue, no study has been designed to determine the best dose and treatment duration of domperidone that ensures both efficacy and patients' safety. In the majority of studies, the domperidone doses used to stimulate lactation were about 10 or 20 mg 3 times a day.<sup>12,16,18,19</sup> However, we must be cautious because some institutions suggest increasing the daily domperidone doses to as high as 120 mg or 160 mg,<sup>22,23</sup> without any clinical validation, and this is twice the maximum daily dose recommended in France.<sup>8</sup> No treatment duration can be defined since they were quite different among the studies, from 4 days<sup>20</sup> to 6 weeks.<sup>16</sup>

### **Domperidone Excretion in Milk**

After a maternal oral dose of 10 mg 3 times a day, an infant would receive a daily dose of 0.2 µg/kg from a daily milk intake of 150 mL/kg and a milk concentration of domperidone of 1.2 ng/mL.<sup>18</sup> After an oral domperidone dose of 10 mg 3 times daily, concentrations in the milk varied from 0.24 ng/mL (1 hour) to 1.1 ng/mL (4 hours) and 2.6 ng/mL (4 days).<sup>24</sup> According to the summary of product characteristics (regulatory drug information for professionals), the concentration of domperidone in the milk of lactating women represents 10% to 50% of the plasma concentrations and is rarely higher than 10 ng/mL.<sup>8,25</sup> After oral doses of 80 mg daily (the highest recommended dose for authorized indications in France), the total quantity of domperidone excreted into milk is less than 7 µg per day.<sup>8</sup>

### **Milk Quality after Domperidone Treatment**

In a randomized controlled trial that included 46 lactating women (22 women treated with 10 mg domperidone 3 times a day for 14 days and 24 controls), the quality of the milk (energy value and quantities of proteins, fats, sodium and phosphate) remained unchanged.<sup>12</sup> Prolactin and carbohydrate concentrations were slightly increased ( $P < .07$ ) and the calcium concentration was significantly increased ( $P = .02$ ) among those receiving domperidone.<sup>12</sup> Consequently, the impact of domperidone on milk quality seems to be limited, except for increased calcium concentration. However, the health consequences of this increase are currently unknown.

### **Maternal Safety of Domperidone**

As mentioned previously, 4 controlled double-blind studies were selected to assess domperidone efficacy (Table 1). Maternal safety was assessed from these 4 publications.<sup>12,18-20</sup>

No side effect was reported in 3 of these studies.<sup>12,18,19</sup> Only the study by Jantarasaengaram et al<sup>20</sup> reported some events of dry mouth in 31.8% of the domperidone treated group and no adverse reaction in the placebo group. These 4 studies assumed that the use of domperidone during breastfeeding was safe, but with a limited number of 60 treated mothers.

### **Domperidone Safety for the Infants**

Among the 7 studies retained,<sup>12,13,16-20</sup> 4 compared the effects of domperidone (30-40 mg/day) to a placebo,<sup>12,18-20</sup> and 5 studies<sup>12,16-19</sup> monitored adverse drug reactions in infants. One hundred and thirteen infants were exposed to domperidone through breastfeeding. No adverse effects were observed in 85 infants, and no information was provided for the remaining 28. The exposure of the 85 infants was heterogenic, according to the dose and the duration of the mother's domperidone treatment. The main dose was approximately 10 mg 3 times a day with a treatment duration between 4 days and 4 weeks. Seven mothers were treated with a dose of 20 mg 3 times a day for 4 weeks.<sup>16</sup> Moreover, infant exposure to domperidone varied according to different factors. Drug concentration in milk is higher at the beginning of lactation, but the mothers included in the studies presented various levels of lactation according to the duration of the pregnancy, the type of delivery, and the length of time since the delivery.<sup>26</sup> Drug exposure through milk depends on the volume of milk ingested, which increases with the age of the infant. Metabolic clearance increases in infants from birth and is equivalent to an adult after 68 weeks post conception.<sup>27</sup> The ages of the infants in the studies varied between 1 day and several weeks.

Bibliographic analysis did not identify any risk for the infants from exposure to domperidone. These studies assumed that the use of domperidone during breastfeeding was safe for the infants. However, these conclusions must be nuanced due to the small number of patients included and the short and disparate duration of treatment (4 days to 6 weeks).

### **Conclusion**

The off-label use of domperidone as a galactagogue is frequent and possibly encouraged by specialists.<sup>4</sup> In an Australian tertiary teaching hospital, dispensation of domperidone to mothers increased from 0.5% in 2000 to more than 5% in 2010, with a mean treatment duration of 12 days for most women (80%).<sup>4</sup> More worrisome is the fact that in most cases (60%), women were not assessed by a lactation consultant.<sup>4</sup>

This review aimed to assess the benefit-risk ratio of domperidone to improve milk production. Domperidone treatment (10 or 20 mg 3 times a day) seems to modestly increase milk production based on the limited data available. The few existing trials seem to demonstrate that maternal treatment with domperidone does not expose breastfed infants to any risk. The presented trials focused on breastfeeding did not report significant adverse drug reactions in the treated mothers.

However, in larger studies focused on gastrointestinal disorders, the use of domperidone is not devoid of risks for the patients. Domperidone is now well defined as a blocker of the rapid component of the delayed rectifier potassium current ( $I_{Kr}$ ; HERG), which in turn is responsible for drug-induced long QT syndrome, arrhythmias, and sudden cardiac death. From the analysis of 5 population-based studies focused on domperidone and cardiac adverse effects, domperidone increased the odds ratio for sudden cardiac death (2.8, 95% confidence interval, 1.53-6.10).<sup>28</sup> The risk of sudden cardiac death seems to be dose dependent, with an odds ratio of 2.57 (95% confidence interval, 0.79-8.36) for patients using 30 mg/day and an odds ratio of 16 (95% confidence interval, 3.49-73.6) for patients using more than 30 mg/day.<sup>29</sup> Moreover, the use of domperidone as a galactagogue is worrisome as drug-induced long QT syndrome occurred mostly in women.<sup>28,30</sup>

The introduction of a drug in these breastfeeding mothers raises other issues that have not been assessed in this specific population. Domperidone is a substrate of the drug metabolizing enzyme CYP3A and of the drug transporter P-glycoprotein, which can lead to drug-drug interactions.<sup>28</sup> CYP3A inhibitors could increase the domperidone exposition and lead to adverse drug reaction, notably cardiac adverse drug reactions.<sup>9</sup> Inhibition of P-glycoprotein can increase the permeability of the blood brain barrier and increase the central nervous system diffusion of domperidone, leading to extrapyramidal side effects.<sup>31</sup>

Finally, the indication of domperidone as a galactagogue drug remains, for now, an off-label use and is still lacking scientific basis.

### Acknowledgments

The authors wish to thank Richard May for the review of the manuscript.

### Declaration of Conflicting Interests

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

### Funding

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

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