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Domperidone and breastfeeding

This document provides information for mothers and healthcare professionals to reach their own decisions. It is not intended to imply recommendations for use of domperidone as a galactagogue nor a dose regimen.

The prescription of domperidone should be avoided in the following situations [1-3];

- **where either mother or baby has any evidence of cardiac abnormalities and specifically arrhythmia**
- **is receiving other medications known to prolong QT interval or potent CYP3A4 inhibitors e.g. quinolone antibiotics, ketoconazole (fluconazole may also be considered a risk), macrolide antibiotics, SSRI antidepressants, tricyclic antidepressants, salbutamol[4]**
- **where severe hepatic impairment has been identified in mother or baby**
- **where either mother or baby has high or low levels of potassium, or low levels of magnesium [4]**

Before prescribing domperidone other measures to increase milk supply should be in place. These include an assessment by someone skilled in breastfeeding support alongside expressing both breasts, at least 8 times in 24 hours including overnight. The maximum dose as a galactagogue should be 10mg three times a day. This prescription should be reviewed at 7 days and further prescriptions should be considered at a reducing dose.

Mothers should be counselled as to the adverse effects of domperidone (abdominal cramping, dry mouth, depressed mood and headache) and advised to report any changes in their baby's behaviour immediately

Domperidone is a drug prescribed for nausea and vomiting. It also speeds emptying of the gut (prokinetic). Until September 2014 it was sold over the counter in the UK. It is not licensed for any indication in the USA because of concerns about arrhythmia. Domperidone has been prescribed off label for babies with reflux.

Following a European Review by PRAC [1] the MHRA updated their advice on the prescription of domperidone in May 2014 [5] (Appendix 1). They advise that domperidone is associated with a small increased risk of serious cardiac side effects. These have been reported predominantly in over 60s who had cardiac problems, were taking other drugs which also cause arrhythmia or were taking a dose of domperidone greater than 10mg three times a day [6, 7].

However:

- We know that breastfeeding and breastmilk are important for optimal health long and short term for mother and baby
- We have research that domperidone increases prolactin levels and milk volume in mothers who have delivered pre term babies and are producing insufficient milk [9-16]

To talk to a mum who knows about breastfeeding call the National Breastfeeding Helpline 0300 100 0212

Calls to 0300 numbers cost no more than calls to UK numbers starting 01 and 02 and will be part of any inclusive minutes that apply to your provider and call package.

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- We have data on the levels of domperidone entering breastmilk and can be confident that these are very low [14-17]
- We do not have research suggesting that domperidone causes risks to otherwise healthy, young women who are breastfeeding [8-16]
- The consensus statement of breastfeeding experts from Canada is that adverse effects to domperidone given to increase lactation are exceptionally rare [8]

So individual prescribing decisions should be made bearing in mind the recommendations of MHRA and the risk to mother and baby of not establishing full lactation

Side effects

Other than those identified by MHRA, side effects are rare – they include stomach cramps, dry mouth, headache and occasionally domperidone is associated with depressed mood (although less than metoclopramide).

Evidence of effectiveness

Domperidone has been used as a galactagogue (to increase milk supply), use for which is off-label, utilising its effect of increasing prolactin. Studies have predominantly been around use in mothers of preterm infants who are struggling to establish lactation 2 to 4 weeks after delivery. The studies have shown that domperidone is effective in increasing breastmilk production. Very small amounts of domperidone pass into breastmilk. The amount depending on the dose that the mother takes. Decision to prescribe for domperidone is the responsibility of the person signing the prescription. This document aims to provide sufficient information for individual decision making bearing in mind the risk to the mother and baby of not breastfeeding compared to the possible risk of the drug. There is no evidence of increased risk to health young women who do not fall into any of the at risk categories [8]

"Of the thousands of mothers the authors of this statement have collectively treated with domperidone for the purposes of breastfeeding support, no one is aware of a single case of maternal death from ventricular arrhythmia. In fact, Health Canada's Canada Vigilance Program has confirmed that between 1965 and 2011, there were no cardiac-related deaths reported among women taking Domperidone"

Osadchy [9] reviewed 3 randomised controlled trials (DaSilva [10], Campbell-Yeo [11] and Petrolagia[12]) involving a total of 78 participants. The results showed a relative increase in breastmilk production of 74.72% over placebo. The study periods varied between 7 and 14 days. Only one study (Petrolagia[12]) referred to lactation counselling prior to prescription of medication or placebo. No follow up data on outcomes after the study period are available.

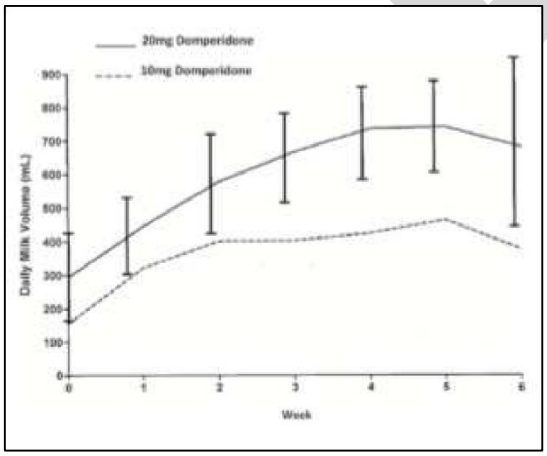


Fig. 1 Milk volume as a function of dose (Reproduced from Knoppert (13)

Knoppert[13] studied pre-terms to determine the optimal dosage of domperidone as a galactagogue randomising women to a regime of 10 or 20mg three times a day for 4 weeks. Following the study period the dose was tapered to a twice daily then daily regime before stopping. At the end of 4 weeks there was no statistically significant difference in the increased milk volumes between the 2 groups but the study was not powered to demonstrate this because of the number of women involved.

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There was a statistical difference in prolactin levels in both cohorts between baseline and day 10. Mothers excluded from the study were those taking anti arrhythmia drugs, who had a family history of arrhythmia, were taking quinolone antibiotics, or drugs metabolised by CYP 3A4 e.g. ketoconazole, macrolide antibiotics. They were required to be pumping a minimum of 8 times in 24 hours. Following the cessation of the drug 4 mothers continued to measure milk volume – 3 maintained their supply one dropped from 750ml per day to 500ml per day. Only one mother exhibited a side effect of nausea which resolved when she took the medication with food.

Campbell-Yeo [(11)] studied the composition of breastmilk following maternal use of domperidone. She analysed the macronutrient content with respect to protein, fat, carbohydrate and energy and macro mineral content of sodium, phosphorous and calcium of 44 women taking either 10mg three times a day of domperidone or placebo. Domperidone increased the volume of breast milk without substantially altering the nutrient composition.

In the DaSilva study [(10)] 20 women in a double-blind, placebo-controlled protocol. Those prescribed domperidone 10mg three times a day showed a steady increase in milk production over placebo. Mothers received counselling support and were double pumping. The increase in production achieved fell once the drug was stopped after seven days. The babies in the study were all in neonatal intensive care and the mothers were only expressing for feeds to be given via naso-gastric tube. The increase in milk volume began 48 hours after the drug was initiated and continued to the end of the trial. The study was stopped after seven days when most mothers began some level of direct breastfeeding, at which point it became impractical to measure breastmilk volume.

Only one study looked at mothers who had not delivered prematurely [(12)]. One month after the study began all treated women had adequate milk production, but none of those who had not been treated with domperidone had achieved an increase in milk supply above that at the beginning of the trial.

Wan et al [(14)] studied seven mothers who had delivered pre-term in a double-blind, randomised cross-over study. They used two dose regimes – 10mg or 20mg three times a day. One mother taking the 20mg dose withdrew early because of severe abdominal cramps. Two others failed to respond to either dose. In four mothers, there was a significant increase in prolactin level and milk volume, with a greater response at the higher dose in three of these women. Side effects noted included abdominal cramping, constipation, dry mouth, depressed mood and headache, which were more apparent with the higher dose. Wan et al (2008) concluded that if there is no response at a 10mg dose, there is no point in further increasing the dose. This is at variance to the information in the consensus statement [(8)].

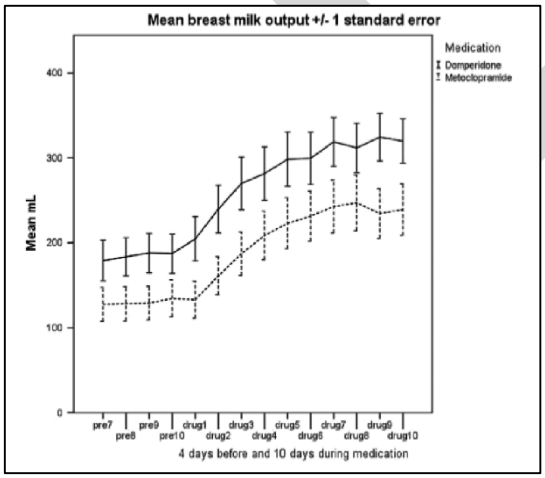


Fig. 2 Average milk output (ml per 24 h) over the medication phase of the study for mothers taking domperidone or metoclopramide (drug days 1–10) and for 4 days before (pre-7 to pre-10). (Reproduced from Ingram [(15)])

Ingram [(15)] studied eighty mothers expressing breast milk for their infants (mean gestational age 28 weeks) based in NICU and the amounts expressed fell short of the infant's needs. Mothers produced more milk in the domperidone group and achieved a mean of 96.3% increase in milk volume compared with a 93.7% increase for metoclopramide. This difference was not statistically significant. Ten women (15.4%) reported 12 side effects when taking the medication. Headache by 1 on domperidone 3 on metoclopramide, 1 on each medication reported diarrhoea, one on each mood swings, one mother on domperidone reported dizziness. Other effects reported by the metoclopramide cohort were change in appetite, dry mouth, and tingling, stinging, uncomfortable breasts. Only one woman stopped taking the trial medication (metoclopramide) after 5 days due to bad headaches and

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dry mouth; all the others tolerated any side effects as they were keen to keep their increased milk production going.

Amount of domperidone in breastmilk

Very small amounts of domperidone pass into breastmilk. DaSilva [16] reported average milk concentrations ranged from 1.2 micrograms/L (1) to 2.6 micrograms/L. in babies whose mothers had taken domperidone 10mg three times a day for 5 days. No adverse events were noted in mothers or children. Domperidone is subject to extensive first pass metabolism which accounts for the low transfer into breastmilk. The mean relative infant dose was 0.01% after a 30 mg daily dose and 0.009% at 60 mg [14]. Hale [17] quotes a relative infant dose range of 0.01% - 0.04%, well below the 10% regarded as significant.

Weaning from domperidone

There are no studies that provide an evidence base on how long to continue domperidone in the case of inadequate lactation [18]. Anecdotally, some women feel that their supply cannot be maintained without the drug, while some can reduce the dose but not stop altogether. It is possible that domperidone is acting as a placebo to boost their confidence – we do not know and should admit the limitations of the research.

After a slow withdrawal from domperidone, one study found no significant increase in formula supplementation suggesting that once sufficient milk production is established, it is maintained even without the use of domperidone [19].

Knoppert [10] showed that in 3 out of 4 women who had taken domperidone for 4 weeks at full dose, 2 weeks at reducing dose, milk supply was maintained. Although gradual weaning from the drug has become standard, there is little evidence apart from the reports and experience of breastfeeding specialists.

Other drugs to increase milk supply

Domperidone is preferred to metoclopramide because it poorly penetrates the blood-brain barrier and does not produce parkinsonian-like adverse effects or increase the risk of depression [17]. The amount passing through breastmilk is significantly less than the dose prescribed directly to babies to control symptoms of reflux.

In Ingram's study [15] ten women (n=65) reported 12 side effects when taking the medication as shown in table 3. Seven of the mothers taking metoclopramide reported side effects and three of those taking domperidone. Only one woman stopped taking the trial medication (metoclopramide) after 5 days due to bad headaches and dry mouth; all the others tolerated any side effects as they were keen to keep their increased milk production going.

Side effect	Domperidone (three women)	Metoclopramide (seven women)	Post-trial metoclopramide
Headache	1	3	0
Diarrhoea	1	1	1
Mood swings	1	1	2
Depression	0	0	2
Feeling dizzy	1	0	0
Change in appetite	0	1	0
Dry mouth	0	1	0
Tingling, stinging, uncomfortable breasts	0	1	0
Restless legs	0	0	1
Itchy skin	0	0	1
Less effective galactogogue	–	–	1
Total	4	8	8

Table 3 reported side effects from trial drugs (reproduced from Ingram)

Review of recommendation on safety of domperidone 2011 in the consensus statement by breastfeeding experts

"The recommendation 2011 (20) is based on data derived from two public health databases: one in the Netherlands (6) and one in Saskatchewan (7). The warning was based on information gathered from an entirely different population than those who would be taking domperidone for breastfeeding purposes and is thus not generalizable to the lactating population.

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The average age of the patients in the studies was 72.5 years in one and 79.4 years in the other. Many of the patients in the studies had pre-existing health problems such as high blood pressure, coronary artery disease, and congestive heart failure. There were, however, some notable trends that, when extrapolated to the breastfeeding population largely comprised of younger healthier women, are quite reassuring. In one study, the authors concluded that the risk of a cardiac problem related to taking domperidone in younger patients was much lower than in older patients. In fact, the risk quoted in younger patients was almost the same as that outcome occurring by chance alone (OR of 1.1 in those younger than age 60 compared with an OR of 1.64 in those older than age 60). That study also specifies that the risk in females was significantly lower than in males (OR of 1.25 in females compared with an OR of 2.23 in males.

The warning regarding the use of domperidone in higher doses (>30mg per day) was based on only one of the two studies; the other study did not include any information about dosing. In the one study where dosing information was included, out of the 1304 deaths that were studied, only 10 patients were taking domperidone at the time of death. Of those 10 taking domperidone, only 4 patients were documented to be taking higher doses of domperidone (>30mg per day). Thus, this Health Canada-endorsed doserelated warning comes from dosing data compiled from a total of four patients. In fact, the authors were not specifically cautioning physicians not to prescribe higher doses, but rather were suggesting that "it is important to avoid prescribing domperidone to patients with a high risk of sudden cardiac death". It is very hard to make a case for a drastic reduction in domperidone dosing in lactating women (wherein a dose of <30mg may not be sufficient to support lactation in a significant number of cases) when the data relied upon to generate the dosing warning was based on such a small number of cases that do not demographically resemble the population in which it is being prescribed. "

Conclusion

Domperidone is not a 'magic wand' to increase the milk supply of a mother struggling to breastfeed, and it should not be used unless accompanied by regular and effective drainage of milk from the breast. It may be a valuable tool to support mothers who have delivered pre-term and who maintain their lactation over a prolonged period by expression, or mothers who have had a poor start to breastfeeding who need to relactate to some extent. It is also useful for women with identified hormonal difficulties that could affect milk supply, e.g. hypothyroid and polycystic ovaries.

Domperidone is a relatively safe drug, but it would be unethical and unprofessional to expose a mother and baby to a drug they do not need, and all measures to improve breastfeeding management should be made and documented prior to a decision to advocate its use.

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Ways to increase breastmilk supply without drugs

Ensure the baby is well attached to the breast and is feeding effectively and frequently

- Encourage and support breastfeeding.
- Listen empathetically to any concerns the mother may have or that have been raised by others who are less supportive of breastfeeding
- Ascertain why she feels she has a low milk supply and address any misconceptions, e.g. reinforce the normality of babies feeding eight to 12 times in 24 hours. Discourage the routine use of dummies if the baby is not feeding frequently enough. Reinforce normality of baby feeding patterns, e.g. 'cluster feeding' in the evenings
- If she feels the baby is unsettled and that this indicates she has a low milk supply, encourage periods of calming skin-to-skin contact or encourage use of a sling to settle the baby. She may also need guidance on feeding the baby lying down at night in order to cope with night feeds
- Observe a complete breastfeed. Check for effective attachment and ensure that both breasts are offered at each feed, with the baby coming off the first breast spontaneously and the breast feeling softer
- Check that the baby's urine and stool output are normal for their age
- Check the baby's weight gain progress
- Check that there are no hormonal reasons why milk supply might be low, e.g. polycystic ovaries, thyroid problems or retained placental fragments
- Question if any medications – prescribed or purchased – are being taken e.g. diuretic, combined oral contraceptive

If the mother smokes encourage her to stop, since nicotine reduces milk supply.

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Appendix 1

MHRA 25 April 2014

Domperidone: risk of cardiac side effects - restricted indication, new contraindications, and reduced dose and duration of use

I am writing to inform you about important new information for domperidone (Motilium).

Summary; Domperidone is associated with a small increased risk of serious cardiac side effects. Its use is now restricted to the relief of symptoms of nausea and vomiting and the dosage and duration of use have been reduced. Domperidone is now contraindicated in those with underlying cardiac conditions and other risk factors (see below).

Background

A recent Europe-wide review has recommended updates to the treatment advice for domperidone following evaluation of the benefits and risks of domperidone (see http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/04/news_detail_00 2083.jsp&mid=WC0b01ac058004d5c1). The review was triggered following continued reports of cardiac side effects and a small increased risk of serious cardiac side effects was confirmed. A higher risk was observed in patients older than 60 years, adults taking daily oral doses of more than 30mg, and those taking QT-prolonging medicines or CYP3A4 inhibitors concomitantly.

Advice for healthcare professionals

Indication Domperidone is now restricted to use in the relief of symptoms nausea and vomiting. It should be used at the lowest effective dose for the shortest possible time

Contraindications Domperidone is contraindicated in people: - with conditions where the cardiac conduction is, or could be, impaired - with underlying cardiac diseases such as congestive heart failure - receiving other medications known to prolong QT or potent CYP3A4 inhibitors - with severe hepatic impairment.

Dose For adults and adolescents over 12 years of age and weighing 35kg or more, the recommended maximum dose in 24 hours is 30mg (dose interval: 10mg up to three times a day). In children under 12 years of age and weighing less than 35kg, the recommended maximum dose in 24 hours is 0.75mg/kg body weight (dose interval: 0.25mg/kg body weight up to three times a day) . The maximum treatment duration should not exceed one week

Non-prescription availability of domperidone:

Domperidone is available to buy in a pharmacy without prescription as tablets for use in adults and adolescents of 16 years and above. It is now restricted to use in nausea and vomiting. It should be used at a dose of up to 10mg three times daily for a maximum period of 48 hours.

Pharmacists are asked to take the following steps when supplying domperidone without prescription: Ask questions to exclude supply for use by people for whom domperidone is contraindicated (see above) • Advise people to take domperidone without prescription only for nausea and vomiting • Advise people to take the lowest dose for the shortest possible time up to a maximum daily dose of 3 tablets and for a maximum period of 48 hours

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