



Statement by The National Infant Feeding Network: December 2014

The use of Domperidone in inadequate lactation

The purpose of this paper is to review and clarify the unlicensed use of Domperidone as a galactagogue, following the statements from the EMA and MHRA in April 2014 (1, 2).

A recent Europe-wide review has recommended updates to the treatment advice for the licensed use of Domperidone, following evaluation of the benefits and risks. 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
- Those taking QT-prolonging medicines or CYP3A4 inhibitors concomitantly (E.g. Erythromycin, Sertraline, Ketoconazole, Salbutamol)

Its licensed use is now restricted to relief of nausea and vomiting and the dose and duration of use have been reduced. It is now contraindicated in those with underlying cardiac conditions and other risk factors.

Although the EMA stated that the scope of the review did not cover use outside the licensed indications (off-label use) it did add that the principles behind these recommendations should be considered whenever Domperidone is used.

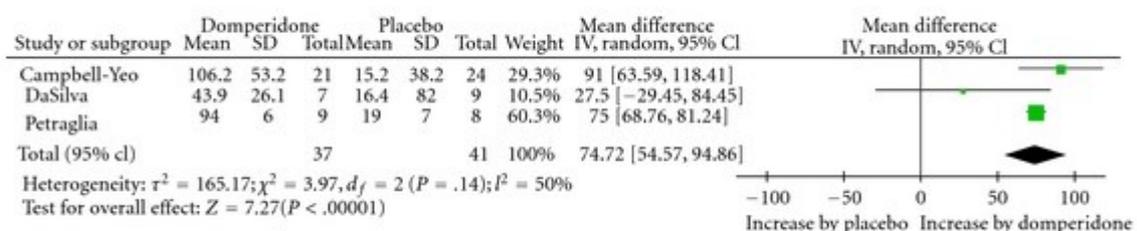
Rationale for the use of Domperidone as a galactagogue

Domperidone is a dopamine antagonist. It works by blocking the receptors for the neurotransmitter dopamine in the gut and in the part of the brain linked to vomiting. Specifically it works on peripheral dopamine receptors in the GI wall and CTZ centre of the brainstem. Prolactin levels are increased as a result of blocking the dopamine receptors.

Unlike Metoclopramide, and most other dopamine antagonists, Domperidone passes poorly into the brain and has thus has few central nervous system side effects, such as depression. Domperidone has a higher molecular weight and binds more strongly to plasma proteins than Metochlopramide, and is thus less likely to enter breastmilk.

Evidence of effectiveness as a galactagogue

Osadchy (2012) conducted a Systematic Review and Meta-Analysis of RCTs which had been conducted to examine the effect of Domperidone on insufficient lactation in postpartum women (3). Three RCTs met inclusion criteria (78 participants), and all showed statistically significant increases in breast milk production following treatment with Domperidone. Analysis of pooled data demonstrated a relative increase of 74.72% in daily milk production with Domperidone treatment compared to placebo.





How much for how long?

General criteria for the administration of any drug, for any reason, would be to use the lowest (effective) dose for the shortest (effective) period of time. This is re-iterated in the EMA / MHRA recommendations.

Dose

In the case of Domperidone used as a galactagogue, the trial evidence suggests that this would be 10 mgs, three times per day (30mgs per 24 hours). This is compatible with the EMA / MHRA recommendations.

Duration of use for nausea and vomiting

Following the EMA / MHRA recommendations, the indications for use are now restricted to nausea and vomiting. It is thus no longer recommended for bloating and heartburn in adults, nor for treating reflux in babies. (However it can still be given to babies to control vomiting.)

For its licensed use, the EMA states that the maximum treatment duration *should not usually exceed one week*. This is repeated on the MRHA website (2).

However in the Department of Health letter sent to health professionals, the word “usually” has been omitted (4).

Nausea and vomiting are symptoms of pathology. The person for whom Domperidone is prescribed for this reason may be ill (e.g. suffering migraine) or be suffering as a result of receiving other medication for an illness (e.g. chemotherapy). In the case of pathology it might be expected that treatment would be reviewed within a week (or less) of the symptoms developing, particularly if they were not resolving.

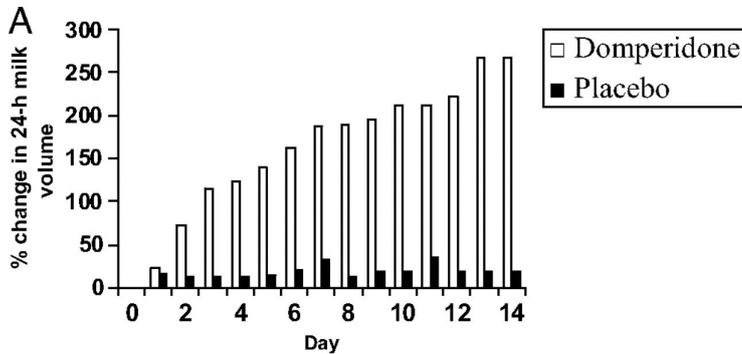
Duration of use as a galactagogue

Data from the trials reviewed by Osadchy (2012) suggest that continuing treatment *beyond a week, up to 14 days*, makes a difference to milk yield.

Author & Year	Dose	Time of measurement	Daily milk yield		Difference
			Experimental	control	
Petalgia et al. 1985	10mgs X 3 days for 10 days	2 nd treatment day	347 +/- 36	335 +/-30	+ 12
		6 th treatment day	636 +/- 59	440 +/- 27	+ 196
		10 th treatment day	672 +/- 44	398 +/- 45	+ 275
Da Silva et al. (2001)	30mgs per day for 7 days	2 nd treatment day	130.4	54.7	+ 75
		6 th treatment day	178.2	57.1	+ 121
		7 th treatment day	183.5	66.1	+ 117
Campbell-Yeo et al. (2010)	30mgs per day for 14 days	1st treatment day	184.4	218	106%
		14 th treatment day	380	250	vs. 15%
			The mean increase in breast milk volume in the Domperidone group was 106% ([380 - 184] x 100/184) and in the placebo group it was 15% ([250 -218] x 100/218). See table below*		

*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 Campbell-Yeo et al. (2010)

Effect of Domperidone on the Composition of Preterm Human Breast Milk (Courtesy of Campbell-Yeo et al, 13)



Women for whom Domperidone is prescribed as a galactagogue are not ill; they will be healthy young mothers for whom there are no contra-indications.

They will also be mothers for whom other methods of increasing milk supply (often for a pre-term baby) will have been unsuccessful. It would seem logical to prescribe the drug at the dose and for the duration supported by the available evidence.

Midlands Medicines, the UK Drugs in Lactation Advisory Service (formerly UKMI) has, from 2006, offered guidance on the use of Domperidone in inadequate lactation in the form of a Q&A sheet on its website (5). The most recent update (2012) offered the following as a summary:

- A health professional should always be involved in the decision to use a galactagogue.
- Drugs to manage inadequate lactation should only be used where there is objective evidence to support diagnosis and where non-drug methods have failed
- There are no drugs licensed in the UK to improve lactation.
- Domperidone is considered to be the agent of choice for inadequate lactation because of its superior side effect profile, efficacy, and minimal passage into breast milk.
- Domperidone should not be used for inadequate lactation where the mother or infant has a cardiac disorder or are receiving treatment with drugs known to affect the QT interval e.g. ketoconazole or erythromycin, in which case metoclopramide is preferred.
- A maternal daily dose of 30mg Domperidone should not be exceeded.
- Further studies are needed to determine the optimum regimen and duration of treatment.

There are insufficient data to support the use of herbal remedies.

This document reviewed the trials included in the Osadchy meta-analysis among many others, but did not give guidance on the optimum duration of treatment. (See above).



Following the EMA statement the following update has been added to the website (6):

“The use of Domperidone to enhance lactation is not specifically covered by the review as it is an unlicensed (off-label) indication. However, the recommendations from the review should apply to its use as a galactagogue.”

“As there are limited alternative options for the stimulation of lactation, the use of Domperidone can be considered provided non-pharmacological options have been unsuccessful.

- *A maternal dose of 30mg daily for a maximum of 1 week should not be exceeded.*
- *Domperidone should not be used if the mother or infant:*
 - *Have conditions where cardiac conduction is, or could be, impaired.*
 - *Are receiving other medications known to prolong QT or potent CYP3A4 inhibitors.*
 - *have severe hepatic impairment.*

If treatment is still required after a week, metoclopramide can be used for up to five days.”

(There is currently no link, and no reference, to support the final statement.)

Comment

The 2012 Osadchy paper (3) concluded that the consistency of the Domperidone effect across the studies (*necessarily in the dosage and for the duration used in the studies*) enhances the confidence of its beneficial effect as a galactagogue.

No maternal or neonatal adverse events were observed in any of the three trials.

The available data indicates minimal excretion of Domperidone into breast milk with extremely low (less than 0.01% of the maternal weight-adjusted dose) infant exposure via breast milk and no side effects have been reported in exposed infants [7–10].

The American Academy of Pediatrics lists Domperidone as compatible with breastfeeding [11]. Furthermore, a 2012 consensus statement by Canadian breastfeeding experts, (which included, amongst others, Daniel Flanders, Aviva Lowe, Michael Kramer, Orlando da Silva, Carole Dobrich, Marsha Campbell-Yeo, Edith Kernerman and Jack Newman) concluded that there is no evidence of increased risk to health young women who do not fall into any of the at risk categories (12).

In the realm of clinical practice, where the balance between desirable and undesirable effects often guides treatment decisions, the current analysis supports consideration that Domperidone might be an effective treatment option for selected women with inadequate lactation.

Many GPs and hospital doctors are well acquainted with the off-label use of medicines in their practice; for example drugs that are only licensed for use to treat epilepsy are frequently prescribed to treat neuropathic pain. In these cases the prescribed dose and duration of the medication may be different from that for the licensed use. In these situations the prescribers take the responsibility for prescribing off-label because they feel the evidence base supports it.

It remains to be seen if this will continue to be the case for Domperidone.



In Summary

- Domperidone should only be considered when all other methods and support for increasing breastmilk are in place.
- A suitably qualified health professional should always be involved in the decision.
- Domperidone should not be used where the mother or infant has a cardiac disorder or are receiving treatment with drugs known to affect the QT interval.
- A maternal daily dose of 30mg Domperidone should not be exceeded.
- For the purpose of increasing milk supply, the evidence supports the use of 10mgs, three times a day, for 10-14 days.
- Ongoing monitoring and support should continue whilst Domperidone is in use and thereafter as necessary.

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