

UKMi Q&A 73.4

Drug treatment of inadequate lactation

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Background

Lactation is the physiological completion of the reproductive cycle. It is a complex process involving physical and emotional factors and the interaction of multiple hormones, the most important of which is prolactin. Oxytocin is involved in the milk ejection reflex (1,2,3).

An intact hypothalamic-pituitary axis regulating prolactin and oxytocin levels is essential for the initiation and maintenance of lactation. Successful lactation requires both milk synthesis and milk release into the alveoli and lactiferous ducts. When milk is not removed, the increased pressure lessens capillary blood flow and inhibits the lactation process. Lack of suckling reduces prolactin release from the pituitary gland. Sensory nerve endings, located mainly in the areola and nipple, are stimulated by suckling. Stimulation of afferent neural reflex pathways via the spinal cord and hypothalamus, produce secretion of prolactin and oxytocin (3). The release and production of prolactin is dependent on the inhibition of prolactin inhibitor factor, which is produced by the hypothalamus and dopamine-releasing neurones (3,4).

As lactation progresses, the prolactin response to suckling diminishes and milk removal becomes the driving force behind milk production (5). This is now known to be due to the presence in secreted milk of a whey protein that is able to inhibit the synthesis of milk constituents (6,7). The definitive indicator of an adequate milk supply is infant weight gain in the early neonatal period (8).

The evidence (9) suggests that when babies are breastfeeding well:

- ◆ Maximum weight loss occurs by 72 hours: "Day 3".
- ◆ Maximum loss of bodyweight is 6-8%.
- ◆ Birth weight is regained by 5-7 days of life.

Causes of inadequate lactation

Since lactation is such a complex process, it is unsurprising that there are a number of causes of insufficient milk supply. A review discussed risk factors for failed lactogenesis (10). While insufficient milk supply is a commonly perceived problem by mothers it actually occurs rarely (8). The most common causes of prolactin deficiency include postpartum pituitary necrosis (Sheehan syndrome) and other causes of anterior pituitary dysfunction, medications (such as dopamine, ergot preparations and pyridoxine) and nicotine.

An apparently low milk supply is one of the most common reasons for discontinuing breastfeeding (11).

Answer

Use of drugs to initiate or augment milk supply

Galactagogues (drugs that promote or increase the flow of a mother's milk) should only be used after thorough evaluation for treatable causes such as poor attachment, and when increased frequency of breastfeeding, pumping or hand expression of milk has not been successful (12).

Indications for the use of galactagogues are (1):

- ◆ Increase of an inadequate milk supply due to maternal or infant illness and prematurity
- ◆ Separation of mother and infant.
- ◆ After a period of milk expression by hand or with a pump when a decline in milk production may occur after several weeks.
- ◆ Adoptive nursing
- ◆ Relactation (re-establishing milk supply after weaning)

Specific galactagogues

There are no products licensed in the UK for use as galactagogues. Such use is “off-label”. There are only a limited number of randomised, placebo-controlled, blinded studies of the use of pharmaceutical galactagogues and few studies meet evidence-based criteria for review (12).

Domperidone

(Prescription Only Medicine (POM), but available as Pharmacy medicine (P) if used for relief of postprandial symptoms)

Over-the-counter (OTC) availability may mean that mothers can self-medicate which is undesirable. A health professional should always be involved in the decision to use a galactagogue.

Domperidone is a dopamine antagonist. Unlike metoclopramide, it passes poorly into the brain and has few central nervous system (CNS) side effects (8), has a higher molecular weight and binds more strongly to plasma proteins (13,14). It produces significant increases in prolactin levels and has proved useful in enhancing lactation (13,15,16) including use in mothers of preterm infants (17,18,19) and critically ill neonates (20) and for augmentation of lactation after caesarean delivery at full term (21). Domperidone is generally well tolerated by treated mothers and fewer cases of dystonia have been reported than after metoclopramide (22). To date, no adverse effects in breastfed infants have been reported (23).

A small crossover study in 6 women with inadequate lactation for their preterm infants compared the effect of domperidone 10mg three times daily with doses of 20mg three times daily. Only 4 of the 6 women responded and there was no significant difference in milk production between the two regimens but side effects were more common in the higher dose group (18). The Academy of Breastfeeding Medicine has observed that there is no clear advantage for dose tapering at the end of treatment (1). Further studies are needed to define the optimal regimen and length of treatment (23).

Concentrations of domperidone in milk vary according to the maternal dose. Following a dose of 10mg three times daily, reported average milk concentrations ranged from 0.28 micrograms/L (18) to 2.6 micrograms/L (8). Because of extensive first pass and gut-wall metabolism, oral bioavailability is only 13-17% (14). The total amount of drug ingested by the infant via milk is very small (about 180 nanograms/kg/day) (24). The mean relative infant dose was 0.01% after a 30mg daily dose and 0.009% at 60mg (18).

The effect of withdrawal of domperidone on subsequent milk production was studied in 25 women given domperidone 20mg four times daily. After a stepwise dose reduction over 2-4 weeks, there was no increased use of formula milk in 23 of the 25 women and normal infant growth was seen in all cases (25). This suggests that once sufficient milk production is established, it is maintained without the use of domperidone.

The U.S. FDA issued a warning in June 2004 about the use of domperidone in inadequate lactation due to concerns over cardiac problems following intravenous use (26). Domperidone can prolong the QT interval. As discussed above, amounts of the drug in milk are very low and lactation experts at the time did not consider the warnings relevant to its use in inadequate lactation (27).

In October 2011, the Pharmacovigilance Working Party of the European Medicines Agency (EMA) issued a summary assessment (28) of the risk of cardiac disorders based on a Dutch study (29) published in the previous year. This suggested that the current use of domperidone, especially at high doses, was associated with an increased risk of serious ventricular arrhythmia (SVA) and sudden cardiac death (SCD). A second case control study (30) involving over 80,000 individuals evaluated the risk of SVA and SCD in users of oral domperidone versus users of proton pump inhibitors on non-users of these medications. The adjusted odds ratio for SVA/SCD for domperidone compared with non-use was 1.59. This increased risk remained after adjustment for multiple co-variables. The EMA advice is that domperidone should be used at the lowest effective dose as it may be linked to an increased risk of SVA/SCD particularly in patients over 60 years or with daily doses exceeding 30mg (28). In the UK, Summaries of Product Characteristics have been amended accordingly (31). 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 (12). A maternal daily dose of 30mg should not be exceeded.

In one study in 46 mothers who delivered infants of less than 31 weeks gestation, domperidone or placebo was given for lactation failure. The effect of domperidone on macronutrient composition of breast milk was also studied (19). By day 14, breast milk volumes increased by 267% in the treatment group compared to 18.5% in the placebo group. Although mean breast protein declined by 9.6% in the domperidone group, changes in energy, fat, carbohydrate, sodium and phosphate content did not differ significantly between the groups. Increases in calcium (61.8% vs. -4.4%) were noted in the treatment group compared with the placebo group. No adverse effects were reported in the mothers or their infants. The authors concluded that domperidone was effective in increasing milk volume of mothers of preterm infants without substantially altering nutrient content. The full significance of the increase of calcium concentration is unclear and requires further study.

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 (32).

Metoclopramide (POM)

Like domperidone, metoclopramide increases prolactin levels via blockade of dopamine receptors. Reports of its successful use as a galactagogue have appeared since the 1980s and it is the agent for which most data have been published (33-37). Metoclopramide has been used in mothers of preterm infants (34,36) and in the intended mother of a surrogate pregnancy (38).

The increase in serum prolactin and milk production appears to be dose-related with daily doses of 30 and 45mg proving effective and 15mg daily ineffective (33). Although metoclopramide does increase milk supply, the effect is very dose-dependent and some mothers do not respond (8). Side effects such as gastric cramping and diarrhoea may limit compliance (8). If no effect is seen within 7 days, it is unlikely that longer therapy will be effective (8). After discontinuation of medication, the milk supply may diminish rapidly and a slow tapering of the dose over several weeks (e.g. by 10mg per week) is recommended in those women who respond (8). Metoclopramide is not suitable for women with a prior history of depression, and use for more than four weeks is not recommended as this may increase the risk of depression (8).

Estimated intake of the drug via milk varies from 1 to 24 micrograms/kg/day. These levels are very low compared to those used to treat reflux in paediatric patients, 100-500 micrograms/kg/day (8). In one study, the plasma prolactin concentration in 4 of 7 neonates sampled during administration of metoclopramide to the mother were higher than the highest plasma prolactin level in infants of the same age with untreated mothers (37).

A recent study was the first to compare the effects of metoclopramide and domperidone on breast milk output of mothers (39). A double-blind, randomised controlled trial in 80 mothers expressing breast milk for their infants (mean gestational age 28 weeks) based in a neonatal intensive care unit, compared the effects of domperidone or metoclopramide 10mg three times daily for 10 days. After adjusting for the amount of milk produced prior to medication, the mean amount of milk produced on medication was 31ml/24 hours greater for domperidone than the mean for those taking metoclopramide. There were small differences in milk output between the two groups and in the incidence of side effects, but these were non-significant.

Sulpiride(POM)

Sulpiride is a selective dopamine antagonist. Limited data suggest successful use as a galactagogue (40,41). The suggested dose to improve milk supply is 10-20mg, orally, three to four times a day (8), although use of higher doses of 50mg twice or three times a day has been reported (40,42). Although significant increases in prolactin are seen, these do not always correlate with increases in milk production (38,39). No adverse effects on breastfed infants were noted in these studies. Reported concentrations in breast milk range from 0.26-1.97 mg/L (8). The estimated infant intake of sulpiride via breast milk has been calculated as 290 micrograms/kg/day (43).

A recent (2012) review in the Cochrane Library assessed the effect on expressed milk volume and duration of breastfeeding of medication for at least 7 days given to mothers of preterm infants whose breast milk was

insufficient for their infants' needs (44). Only 2 studies involving 59 mother-infant pairs met the inclusion criteria although other uncontrolled studies were included in the initial assessment. Modest improvements in expressed breast milk (EBM) was seen when domperidone (10 mg tds given for 7 – 14 days commencing at or after 14 days post pre-term delivery) was given to mothers with insufficient EBM with other lactation support. Neither study showed significant improvements in long term outcomes. None of the currently reported trials of medications to increase breast milk volume have examined effects for more than 14 days. The timing of introduction of medication remains controversial. Currently, no studies support prophylactic use of a galactagogue at any gestation.

Herbal medications

Various herbal remedies, including milk thistle and fenugreek, have been suggested to improve poor milk supply. However, there is insufficient evidence of safety or efficacy to recommend such use (45,46). There may be concerns over the relative potency and quality control of herbal products (8).

Other

In one small study, 19 puerperal women with inadequate lactation (less than 50% normal milk yield) were randomised to receive thyrotrophin-releasing hormone (TRH) 1mg (n=10) or placebo (n=9) four times daily by nasal spray for 10 days, starting on day 6 postpartum. Milk yield increased significantly in the active treatment group whilst there was no significant change in the controls. A further rise in prolactin and milk yield was seen in seven of the TRH treated group given a second 10-day course at their own request. No significant changes in levels of TRH, thyroxine or tri-iodothyronine were seen in either group (47).

Small studies have been conducted on the effects of oxytocin (48,49) and somatropin (50,51) on human milk production but there is insufficient experience to recommend their use as galactagogues

A single session of acupuncture had variable effect in 90% of 30 women with postpartum inadequate lactation. Improved lactation was more marked after 3-5 sessions, especially in primiparae, within 10 days of delivery. Acupuncture was less effective the longer the duration of inadequate lactation (52). Similar positive outcomes were seen in a study of two courses of acupuncture in 96 mothers (53). Acupuncture was also effective at maintaining breastfeeding until infants were age three months in a study of 90 mother-infant pairs (54).

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.

Limitations

Published reports of drug use in lactation are generally limited to small numbers of subjects or to single case reports. Quantitative reports are often limited to single time point estimations. Many of the studies were performed before the introduction of modern lactation management. Few studies have provided encouragement and instruction to mothers. There are often inconsistencies in inclusion criteria that could minimise possible differences between drug and placebo groups (18).

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Search strategy

- Medline search 1951 – date 13/04/2010
 1. LACTATION – DISORDERS.DE. with DT
 2. LACTATION W..DE
 3. (1 OR 2) and human = yes
 4. domperidone.w..de.
 5. 3 AND 4
 6. METOCLOPRAMIDE.W..DE.
 7. 3 AND 6
 8. SULPIRIDE.W..DE.
 9. 2 AND 8

- Embase search 1974 – 13/04/2010
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 2. LACTATION.W..DE.
 3. (1 OR 2) AND HUMAN = YES
 4. DOMPERIDONE.W..DE.
 5. 3 AND 4
 6. METOCLOPRAMIDE.W..DE
 7. 3 AND 6
 8. SULPIRIDE.W..DE.
 9. 3 AND 8

- Cochrane Library
- General Internet search per Google – lactation disorders/inadequate lactation
- Natural Medicines Comprehensive Database accessed 18/08/2005,04/01/2006 and 13/04/2010
- In house resources (past enquiries, database)
- Clinical experts : Sally Inch, Infant feeding Specialist, Human Milk Bank and Baby Friendly Co-ordinator, Womens' Centre, Oxford Radcliffe Hospitals NHS Trust, Peter Golightly, Director, Trent Medicines Information Service
- UKDILAS database