



Charles Darwin University

Domperidone as a galactagogue

A case for approval?

Nel, Steffne; Geraghty, Sadie

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Domperidone as a Galactagogue: a case for approval?

Abstract

A common concern expressed by women to health professionals providing care during their pregnancy and in the postnatal period is whether they will be able to produce enough breast milk to meet the nutritional requirements of their baby.

Galactagogues are defined as substances, including drugs and foods, which promote lactation. This term encompasses therapies which have been clinically proven, alongside remedies which have limited current evidence to support the claims associated with them. Domperidone is an antiemetic drug that is gaining in popularity and use as a galactagogue.

Clinical manifestation

The aetiology of poor lactation is complex and multifaceted and should be evaluated and assessed on an individual basis. The most common and easily rectified factors involved with lactogenesis, and impaired milk supply, are related to inadequate stimulation of breast tissue due to position and attachment at the breast and infrequent/delayed feeding (McDonald and Magill-Cuerden, 2011). Women with preterm neonates in a hospital nursery are more prone to lactation insufficiency and heavy reliance on breast pump use (Haase et al., 2016). Another potential contributing factor to difficulty in achieving adequate milk supply is insufficient

glandular tissue in the breasts, known as hypoplasia (McGuire and Rowan, 2015).

Other medical conditions which may cause disruption impacting upon lactation and ability to establish an adequate milk supply include poor maternal nutrition; nipple trauma, significant anaemia, polycystic ovarian syndrome, thyroid disease, diabetes, pre-eclampsia, and retained uterine products, mother-newborn separation, tongue tie, congenital anomalies such as cleft lip/palate and chromosomal disorders (De Bortoli and Amir, 2016, Chu et al., 2016, Bergmann et al., 2014). It has also been suggested that epigenetics may influence breastfeeding experiences (Porta et al., 2016).

Domperidone pharmacology

Domperidone is an antiemetic drug which has been approved for the use in the treatment of gastroparesis (idiopathic or diabetic), nausea and vomiting, and acts on the central nervous system as a selective D2 dopamine receptor antagonist (Doggrell and Hancox, 2014), and blocks chemoreceptors located in the fourth ventricle (Lang et al., 2012). It is also schedule four drug which is prescription only medication; when administered orally, relatively rapid absorption results in peak plasma levels occurring within 30 minutes of administration and undergoes prompt hepatic metabolism resulting in system bioavailability of approximately 13-17% of the dose (Lang et al., 2012). Domperidone is distributed by binding with plasma proteins, and in healthy individuals, the half-life of a single oral dose is between seven and nine hours (Hill et al., 2015). Domperidone does not cross the blood brain barrier,

therefore, has minimal effects on the central nervous system (Grzeskowiak et al., 2015).

Domperidone as a galactagogue

One of the observed side effects of the use of Domperidone is increased prolactin levels, and which sparked interest in its potential to be used as a galactagogue, for women with lactation insufficiency related to low prolactin levels resulting in reduced milk supply (Hondeghe and Logghe, 2016). The dopamine antagonist properties of Domperidone is beneficial to enhancing lactation due to dopamine being the main inhibitor of prolactin release (Paul et al., 2015). Prolactin is a hormone secreted by the anterior pituitary gland which is involved in stimulating lactogenesis and maintenance of milk production and supply through a supply and demand principle regulated by infant suckling and breast stimulation (Gustafson et al., 2016).

Despite stating that the potential amount of Domperidone that may be transferred to newborns through breast milk is extremely low, the manufacturer product information sheets cite the limited knowledge regarding whether Domperidone may cause harm to the newborn, as the rationale for the recommendation that women taking Domperidone should not breastfeed. Difficulties arise when attempting to understand and quantify what constitutes an extremely low levels of the drug which the newborn is exposed to, as factors such as the variations in amount of milk transferred at each feed, the type and composition of milk such as colostrum, transitional, fore/hind and differing fat content need to be considered. Despite these

variables of breast milk composition and volumes Paul et al. (2015) note that a randomised control trial found that apart from increased prolactin and carbohydrate levels, there was no significant change to milk composition with the use of Domperidone. It has been suggested that it is possible to achieve therapeutic benefits, by standardising and using prescribing protocols widely agreed upon by expert clinicians regarding the safe use of Domperidone in lactating populations, including pharmacological intervention that should only be considered after first line breastfeeding interventions have been exhausted (Osadchy et al., 2012). Identified potential risks can be reduced by formulating and implementing standardised clinical guidelines, which support the use of Domperidone as a safe and effective option for women with sub optimal lactation, within parameters and known health outcomes outlined by existing research findings, which acknowledge the age and general health status of childbearing and lactating women (Haase et al., 2016). A retrospective cohort study, that reviewed prescribing rates of Domperidone amongst Canadian women in the postnatal period, found that between 2002 and 2011, the prescribing trend for this population increased from 8% to 19% respectively for term births and from 17% to 32% for preterm births respectively (Smolina et al., 2016). The authors of this study questioned whether adequate efforts to promote and encourage women to engage in non-pharmacological alternatives were being neglected by prescribers, but also noted that exclusive breastfeeding rates had also increased exponentially from 28% to 41% during the same time period. Therefore,

further examination of current prescribing trends is required, to establish if these rates continue to be reflected in current practice.

Alternatives to Domperidone

Metoclopramide is another dopamine receptor antagonist that has also been used as a galactagogue, but unlike Domperidone, it crosses the blood brain barrier and has been linked with an increased risk of extrapyramidal side effects compared to the risk associated with Domperidone (Grzeskowiak and Amir, 2015). Metoclopramide levels in expressed breast milk have been observed to be similar to maternal plasma levels, and neonatal serum levels indicate that metoclopramide is transferred to the neonate in breast milk which may also have an accumulative effect in neonates (Sachs, 2013).

The use of intranasal oxytocin to stimulate the let-down reflex was first described in a seminal study which reported that although there were some mild side effects, "the method may be a useful aid to breastfeeding where milk ejection is inhibited" (Newton and Egli, 1958). This method of lactation augmentation was studied further, following the development of synthetic oxytocin, using a nasal spray which was self-administered by women prior to commencing a feed (Stewart, 1961). The study found this intervention improved milk production with no reported side effects, and also concluded that the accepted scientific understanding at the time regarding oxytocin triggering the release of prolactin, was inaccurate.

Non-pharmacological approaches to enhance physiological prolactin release are preferred and recommended (Rai et al., 2016). Strategies such as early initiation of skin to skin contact, establishing an agreed indirect (i.e. hand or pump expressing) lactation regime with a hospital grade breast pump, in addition to the provision of breastfeeding education and support services, are interventions often adequate to achieve an increase in milk volumes. Stewart (1961) observed "The milk let down reflex is usually normal in all relaxed unemotional mothers, but the tensions of today's world are not conducive to this attitude" (pg 1072). Psychosocial factors remain a significant factor for women who perceive their milk supply to be insufficient for the nutritional needs of their newborns, which highlights the importance of reassurance, education, emotional and practical support provided by health professionals.

While there is some anecdotal evidence for herbal remedies with reported galactagogue properties, peer reviewed studies supporting these claims are limited (Haase et al., 2016). Herbal remedies and preparations are not as stringently regulated as pharmaceuticals, and the concentrations of herbal components may differ between preparations (Sachs, 2013). There are numerous foods and substances with galactagogue associations, while some herbal remedies are preferred over others due to intergenerational use, depending on cultural backgrounds women identify with (Knoppert et al., 2013). Some well-known non-pharmacological galactagogues include fenugreek, goat's rue, milk thistle, and lactation cookies containing brewer's yeast; which all currently lack rigorous scientific testing to

support claimed properties (Rosalle, 2015). Fenugreek is a herb, and while there is limited current scientific evidence which supports claims of its lactation inducing properties, animal studies have been conducted which provided some positive results to support its use and justification for further trials in human populations (Sharma et al., 2014). Another alternative practice gaining secular popularity is placentophagy, where the placenta is usually dehydrated and encapsulated for ingestion (Cole, 2014). However, there is limited contemporaneous literature which provides evidence of placenta as a proven and effective galactagogue, and more rigorous research is required to determine if such benefits exist.

Herbal supplements and alternative therapies have potential side effects for both the woman and newborn, so need to be taken in consultation with health professionals who possess appropriate knowledge of their components, safety, contraindications and their use in regards to lactation and breastfeeding (Kavurt et al., 2013).

Potential complications for women and newborns

The benefits of breastfeeding for both mother and baby are well documented and widely accepted by health care professionals, with the significant neurodevelopmental benefits, and role in reducing rates of morbidity, such as the incidence of necrotising enterocolitis and sepsis, in hospitalised pre-term newborns for part of the rationale for the preference of breast milk over breast milk substitute formulas (Asztalos et al., 2016). When health professionals are discussing commencing any drug therapies with women who are already breastfeeding, or

planning to breastfeed, the risks, benefits and compatibility of both breastfeeding and pharmaceutical intervention need to be carefully considered according to each individual woman and her baby's history. The complexity of this task, coupled with limited knowledge surrounding pharmacology and breastfeeding, can at times result in some health professionals applying generic recommendations, such as avoiding all medications for breastfeeding women or in contrast that women taking medications shouldn't breastfeed, when in most cases the benefits of taking the medication and breastfeeding outweigh the risks (Nice and Luo, 2012).

Contraindications and precautions which need to be considered prior to prescribing Domperidone include maternal history of hepatic and renal impairment, prolactin-releasing pituitary tumour (prolactinoma) and past history of breast cancer, gastrointestinal conditions where increased gut motility may result in haemorrhage, obstruction, and/or perforation (Hall, 2016). Common side effects of Domperidone reported by 1% of users include dry mouth and headache, and other rare 0.1%, but significant reported side effects of Domperidone include severe allergic reaction, increased somnolence, extrapyramidal symptoms/side effects, and severe cardiac complications (Parkman et al., 2011). Drowsiness and dizziness may be of particular concern to postnatal women, as this may increase risk of maternal or neonatal injury and/or harm in relation to falls or unintentional co-sleeping.

Safety concerns have been raised regarding Domperidone and the increased risk of serious cardiac arrhythmias and sudden cardiac death related to drug induced prolonged QT intervals (a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle). It is important to note that adverse events have been reported in cases in where the daily dosage exceeds 30mg, was administered via intravenous route, and the individuals were 60 years and over (Schaefer et al., 2014), which are not comparable clinical situations to the demographics and general health status of women taking Domperidone to promote lactation. In light of documented adverse outcomes, Domperidone is contraindicated for women with known previous histories of cardiac arrhythmias or cardiac disease, and/or are also currently taking prescribed medications which prolong QT intervals, including CYP3A4 (enzymes involved in drug metabolism) inhibitors (Grzeskowiak and Amir, 2015). No cases of sudden death related to prolonged QT intervals have been reported in lactating populations internationally, although women still need to be made aware of potential side effects and complications, such as cardiotoxicity, the medical conditions which may increase their risk of adverse outcomes, in addition to the signs and symptoms of these complications which would indicate the immediate cessation of Domperidone and to seek further medical advice.

In regards to the newborn, the effects or potential harm caused as a result of exposure to Domperidone ingested via breast milk are unknown, and arguably such evidence becoming available in the future is unlikely as the ethical approval to conduct research that would be required to study such effects would attract such

scrutiny that would prevent approval being granted. Currently the general consensus from the observational evidence available is that the amounts of the drug transferred to the newborn through breast milk are negligible, and there have been limited documented reports of complications as a result of exposure (Haase et al., 2016). Some assert that the benefits of establishing a sufficient supply in order that the newborn is able to receive breast milk, in particular pre-term neonates, remains the optimal enteral nutrition and therefore outweighs the potential risks of exposure to Domperidone. The long term benefits of breastfeeding, for both the mother and her newborn, outweigh the relatively minimal maternal and neonatal risk and that restricting its use within current recommended guidelines would be doing women and newborns a disservice and potentially denying them of the benefits of breastfeeding.

Conclusion

Domperidone continues to be a popular and viable treatment recommendation for low milk supply during the postnatal period. The dopamine antagonist properties of Domperidone has been shown to be beneficial to enhancing lactation due to it being the main inhibitor of prolactin release, that stimulates lactogenesis and maintenance of milk production, through a supply and demand principle regulated by infant suckling and breast stimulation. However, there is limited evidence to assure the safety of exposure of newborns to the drug through ingested breast milk.

Breastfeeding is the gold standard of infant nutrition which should be promoted and

enabled wherever possible, therefore there is sufficient justification for further research to evaluate the actual or theoretical risks of adverse outcomes associated with the use of Domperidone, such as significant cardiac comorbidities, in order to establish evidence based practice guidelines in lactating populations. Prior to referring women for prescriptions of Domperidone, midwives, nurses and health visitors should consider whether appropriate preferred non-pharmacological strategies have been considered and implemented first, and if she has any medical conditions which would contraindicate the use of Domperidone, to evaluate if pharmacological intervention is indeed warranted.

Highlights

One of the observed side effects of the use of Domperidone is increased prolactin levels, that has promoted its' use as a galactagogue
Domperidone is distributed by binding with plasma proteins, and in healthy individuals, the half-life of a single oral dose is between seven and nine hours
The dopamine antagonist properties of Domperidone is beneficial to enhancing lactation due to dopamine being the main inhibitor of prolactin release
There is no significant change to milk composition with the use of Domperidone
Contraindications and precautions which need to be considered prior to prescribing Domperidone include maternal history of hepatic and renal impairment, prolactin-releasing pituitary tumour (prolactinoma) and past history of breast cancer, gastrointestinal conditions where increased gut motility may result in haemorrhage, obstruction, and/or perforation
Common side effects of Domperidone include dry mouth and headache, and more serious side effects include severe allergic reaction, increased somnolence, extrapyramidal symptoms/side effects, and severe cardiac complications

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