Hot Topic

Is there a future for domperidone to help breast milk supply? A review of the evidence

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ORIGINAL

Background

The World Health Organization (WHO) recommends babies should be breastfed or receive breast milk exclusively for the first six months and, in addition to a varied diet, for up to two years and beyond (WHO 2021). In the United Kingdom (UK) evidence shows under half of mothers are using breast milk at six to eight weeks postpartum and only one per cent of babies are receiving breast milk at 12 months old (Public Health England 2020).

As a breastfeeding peer supporter I often support women who are struggling with a perceived low milk supply and have considered whether the use of a drug that has a known non-intended side effect of increasing breast milk supply — domperidone — should be explored.

In this paper I review the risks of domperidone against the benefits of continued breastfeeding by investigating the pharmacology, ethical and legal considerations, the role of the midwife, and the literature surrounding domperidone.

What is domperidone?

Domperidone was first synthesised by a Belgian company, Janssen Pharmaceutica, in the early 1970s. Antipsychotic medicines were discovered to affect dopamine receptors and frequency of vomiting (Sneader 2005). However, patients also developed undesirable neurological side effects, known as extrapyramidal effects. To alleviate these side effects, and act as a reliable anti-emetic, Janssen Pharmaceutica attempted to develop a dopamine antagonist that failed to cross the blood-brain barrier.

Domperidone was known and marketed as 'Motilium' in West Germany and Switzerland from 1979 and from 1982 in the UK. In 1999, domperidone was produced as an orally dissolving tablet. Domperidone can also be administered intravenously or intramuscularly (IM) due to a common side effect of xerostomia ('dry mouth'), which may affect oral administration (National Health Service (NHS) 2020a).

Historically domperidone was prescribed as an anti-emetic in children. However, in a randomised controlled trial (RCT) of 292 participants, Leitz et al (2019) found no significant difference between the intervention and the placebo in paediatric patients and, due to the side effects of domperidone, suggested alternative medicines would be a preferred option. Consequently, the Medicines and Healthcare products Regulatory Agency (MHRA) recommended that domperidone's licence be removed for use in children under 12 years of age or weighing less than 35kg due to insufficient research (MHRA 2019).

Domperidone as a galactagogue

Side effects are secondary symptoms caused by medicines, differing from adverse reactions. At times, the side effects are the rationale behind the prescription. All medicines have the potential to cause side effects, including General Sales Licence (GSL) medicines, herbal remedies, and supplements (NHS 2018) and should be supplied with a patient information leaflet (PIL) outlining side effects and the likelihood of developing them.

Side effects of domperidone include a dry mouth, anxiety, asthenia, breast abnormalities, gastrointestinal (GI) complications, lactation disorders and cardiac complaints (Joint Formulary Committee 2020).

Domperidone as a galactagogue is interesting as it is prescribed and administered based on a side effect, rather than its primary use.

Use of domperidone in pregnancy

A Canadian study reported over 2,000,000 prescriptions for domperidone for gastrointestinal use in 2014 (Bustamante-Bernal et al 2015). The prevalence of usage of domperidone in Canada suggests the possibility for research into the use of domperidone as an anti-emetic in pregnancy.

The evidence-based prevalence of domperidone usage in the UK is seemingly unreported. However, it is reasonable to postulate a similar level of usage as that in Canada to the UK, based on the ethnocentric demographic; a predominantly White population in a developed country with, on average, 650,000 births each year (Office for National Statistics (ONS) 2020).

A teratogenic effect occurs when medication crosses the placental barrier; drugs with a molecular weight of more than 500g/mol do not cross the placental barrier. Domperidone has a molecular weight of 425.9g/mol and, therefore, crosses into the placenta, exposing the fetus to potential teratogenicity (National Center for Biotechnology Information 2005).

Michiels et al (1981) studied the absorption, distribution, and metabolism of domperidone in pregnant and lactating rats. They concluded that the drug passes across the placenta and to the infant rat via breast milk (Michiels et al 1981). Their results could be applied to humans as both species are classified as mammals and placental function and lactation mechanisms are similar. However, the age of the study limits its reliability and further research is needed.

Interestingly, Choi et al (2013) suggested no significant teratogenic effect of domperidone use in 120 participants and is supported by recommendations from Pregnancy Sickness Support; one of the UK's leading charities supporting pregnant people suffering from hyperemesis gravidarum. Research is however limited into domperidone use and teratogenic effect despite prescription use for many years with no negative impact on the fetus reported (Pregnancy Sickness Support 2020).

Pharmacokinetics — how the drug moves within the body

Absorption

The absorption of a drug is dependent on the administrative route: 'enteral' — via the GI tract or 'parenteral' — via the skin or spinal canal. Domperidone can be administered via both routes.

With oral administration the drug is predominantly metabolised by the liver and the intestines. As a result, domperidone undergoes the first pass effect, whereby the concentration of the drug is decreased before it reaches systemic circulation. This causes bioavailability to be low, at approximately 13–17 per cent. However, when administered through intramuscular injection, bioavailability reaches 90 per cent (Reddymasu et al 2007). This finding is significant for the population of pregnant people for whom oral anti-emetics are less effective.

Distribution

Domperidone is bound to the proteins in blood plasma; the amount bound has an overall effect on the efficacy of the drug. Domperidone has a binding rate of 91–93 per cent; the small percentage of active domperidone that remains unbound can be metabolised and excreted by the body (Aurobindo Pharma - Milipharm Ltd 2019).

Metabolism

With oral administration, domperidone is absorbed within the GI tract and passes, via the hepatic portal system, to the liver where it is metabolised, allowing it to be excreted more readily (Tortora & Grabowski 1999).

Excretion

Excretion occurs via the renal, biliary and respiratory system, and breast milk. There is limited research showing that less than 0.1 per cent of the dosage is transferred via breast milk and no adverse effects have been reported. However, the possibility of adverse effects cannot be eliminated (Drugs and Lactation Database (LactMed) 2020). Higher level research is required, however, in view of the currently

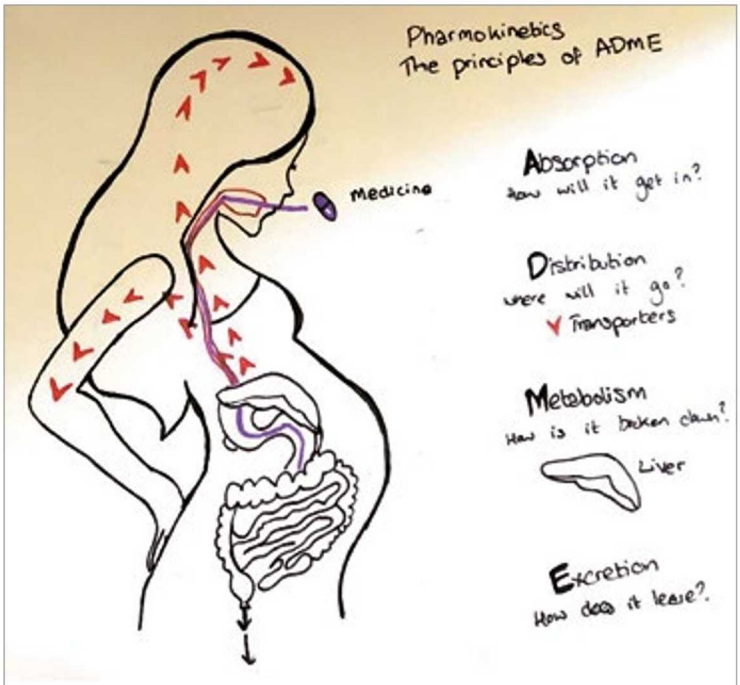

Figure 1. Pharmokinetics: the principles of ADME.

available evidence, the British National Formulary (Joint Formulary Committee 2020) suggests that the amount consumed by the neonate is too small to be significantly harmful.

Pharmacodynamics – what the drug does to the body

The mechanism of domperidone occurs outside of the central nervous system as it is unable to cross the blood-brain barrier. Side effects are less likely to be linked to the brain and/or spinal cord and therefore, experienced in a localised area or system.

Inhibiting or activating receptors is how medication causes an effect. Domperidone is a receptor antagonist, meaning it blocks or reduces a response by binding to the receptor.

The affinity of the drug needs to be high in order for binding to occur, this is done via a ligand which binds to the receptor protein; forming a receptor-ligand combination. Domperidone does this well, resulting in high affinity to the dopamine D2 and D3 receptors.

Gastric changes

A pro-kinetic agent increases the frequency and strength of peristalsis by blocking dopamine receptors in the upper region of the GI tract, causing contractions of the pyloric sphincter and the stomach. Irritants, such as medication or hormones, trigger nerve impulses in the stomach which are received by the chemoreceptor trigger zone (CTZ), stimulating signals to the area postrema, also known as the vomiting centre of the brain. By blocking the dopamine receptors in the CTZ, signals to the area postrema are inhibited, reducing nausea and vomiting (Sui et al 2020).

Chemoreceptor trigger zone

Located outside the blood-brain barrier in the medulla oblongata, the CTZ receives input from drugs or hormones in the systemic circulation. The CTZ is linked to the area postrema, which houses receptors for dopamine, histamine, serotonin, and opioids. This may explain why opioids often lead to feelings of nausea and/or vomiting, a consideration during prescription.

Prolactin levels

Domperidone can increase breast milk yield by increasing prolactin levels. Produced and secreted by the anterior pituitary gland, prolactin is a protein molecule found in mammals, crucial to lactation. In a small study, Wan et al (2008) found an increase in breast milk supply in two-thirds of women, suggesting a direct correlation between the use of domperidone and an increase in breast milk supply. However there has been research that shows an association between domperidone and an extended QT interval on electrocardiograms (Paul et al 2015). Therefore, further research into the use of domperidone as a galactagogue, and the longitudinal effects on the QT interval of mothers and neonates, is required.

Pharmacogenetics – how genetics affect response to the drug

Pharmacogenetics is a contemporary field of study that uses genetics to predict outcomes in response to therapy, allowing prescribers to individualise care. By monitoring pharmacological variability, it is possible to predict the outcomes of drug administration while maximising efficacy and minimising toxicity. Domperidone has been known to have different effects in people with polymorphisms in the transporter gene ABCB1 (this encodes P-glycoprotein) (Parkman et al 2011).

Effects on the fetus/neonate

Research on the effects of domperidone on the neonate has shown that the main concern is the elongated QT interval; the time taken for the heart to undergo ventricular repolarisation. Günlemez et al (2010) found that, if an elongated QT interval occurs, the likelihood of a significant, clinical side effect is small. However, this was a small study of only 40 neonate participants, thus indicating the requirement for further research.

A very small amount of domperidone is excreted via breast milk (1.2 micrograms/L (1) to 2.6 micrograms/L): an amount unlikely to cause any significant harm to the neonate. One must counter this with the many positives should the administration of domperidone result in the continuation of breastfeeding.

Breast milk is designed specifically for the neonate, containing antibodies relating to pathogens to which the baby and mother have been exposed (Zheng et al 2020). Breastfeeding can also decrease the risks of diarrhoea, vomiting and constipation, sudden infant death syndrome, obesity, diabetes, and cardiovascular disease (NHS 2020b).

Research suggests that the amount of domperidone consumed via breast milk is minimal. The drug is safe to administer as the benefits of breastfeeding outweigh the risks of the drug. However, more research with large sample sizes could be done on the topic to ensure a wider and more comprehensive understanding.

Contraindications to domperidone

Due to the elongation of the QT interval, individuals suffering from impaired cardiac function, or conditions affecting cardiac electrical activity, should seek a review from their doctor. Individuals suffering from underlying cardiac disease, or taking medications known to affect the QT interval, should seek advice before the consumption of domperidone (MHRA 2019).

Regarding hepatic impairment, prescription and administration of domperidone should be considered carefully due to the unbound fraction of domperidone increasing by 25 per cent in hepatically impaired patients (Zentiva 2020).

Ethical considerations

The ethics surrounding drug administration should be at the forefront of a practitioner's mind. The code of conduct states that midwives should practise in an ethically sound way; prioritising people, practising effectively, preserving safety, and promoting professionalism (Nursing and Midwifery Council (NMC) 2018).

Having an in-depth understanding of individuals in one's care, and the skills and knowledge of how to determine their medical history is crucial when prescribing and administering medication. Additionally, a good understanding of the medication, pharmacology and contraindications is required to ensure safe, ethical practice.

When domperidone is prescribed to increase breast milk supply, there are ethical implications as it would be prescribed 'off-licence'. The patient should be aware of the risks, benefits and implications of unwanted side effects or adverse reactions. When being used 'off-licence', the prescriber, whether a midwife with extended prescribing authority or another medical professional, is accountable for the administration of domperidone, and therefore, it should be carefully considered before the prescription.

Legal considerations

Maternity is the clinical area with the highest cost of legal claims (Vernon 2019). The law seeks to regulate the safety of administration and ensure a high standard is adhered to. The Medicines Act (1968) is the legal framework covering the manufacture, distribution, and availability of all medicinal products.

Drugs are categorised into three groups: prescription-only medications (POM), pharmacy medications (P) and general sales list medications (GSL). POMs are the most restricted, supplied by a pharmacist and prescribed by a doctor or another medical professional with prescribing qualifications, they represent a direct danger to the patient if prescribed or administered incorrectly (The Prescription Only Medicines (Human Use) Order 1997). Domperidone falls into this category.

Some medications can be administered by an appropriate practitioner under a Patient Group Directive (PGD). There is no requirement for a prescription from a registered prescriber but there needs to be an advantage to the patient without compromising their safety, for example, midwives may administer the flu jab under a PGD. However, the use of domperidone for the increase of breast milk supply is an unlicensed action (MHRA 2017) and the unlicensed support of medication under a PGD is prohibited.

What does this mean for midwives?

According to The Human Medicines Regulation (2012), midwives can supply all GSL and P medications if they are outlined in the Midwives Exemption, with prescriptions required for other medications. If a midwife and/or nurse has completed an NMC-approved independent and supplementary prescribing qualification, they can prescribe medicines not listed within the Midwives Exemption, as long as they remain within the limits of the qualification.

Midwives are often the first point of call for women experiencing breastfeeding problems. All medication use in pregnancy and lactation must have a benefit that outweighs the risk when considering prescription. It is vital that the prescriber is aware of the indications and contraindications and considers whether there are any suitable alternatives available. After all other options to increase milk supply have been exhausted, having an understanding of domperidone and its effects could be the difference between a mother ceasing to breastfeed and continuing their journey.

A midwife would be able to liaise with a multi-disciplinary team of doctors, health visitors, and infant feeding specialists to ensure that a prescription and adequate support are provided if the mother wants to continue breastfeeding.

Conclusion

There is little research into the effects of domperidone as a galactagogue. However, there is plenty of research into attitudes around breastfeeding. Research shows a direct link between domperidone and cardiac complications in mothers and neonates. However, these complaints are minimal and usually have no clinical significance. Interestingly, there have been no reported cardiac complications in neonates who have been breastfed by mothers taking domperidone.

Brown et al (2015) suggest the early cessation of breastfeeding is linked to the development of postnatal depression. In a study of 217 women with infants aged 0 – six months all participants had initiated breastfeeding but stopped before their children reached six months of age and this linked to postnatal depression.

By supporting mothers to reach their breastfeeding goals and to cease breastfeeding at natural term, or at a time that is convenient and determined by them, midwives and health care professionals can make a direct contribution to a reduction in the prevalence of postnatal depression. Supporting informed choices for women in their infant feeding goals can have

a direct impact on the mental health of mothers across the country. This is an important public health matter, given that 15 per cent of women in the UK are affected by postnatal depression (Green 2018). By supporting their journeys and ensuring that they have access to education and help throughout the childbirth continuum, midwives and health visitors can improve the health of the next generation and beyond.

In the context of the COVID-19 pandemic, the continuation of breastfeeding is arguably more important than ever. With breastfeeding directly protecting children against viruses and pathogens, perhaps now is the time to revisit the use of domperidone as a galactagogue with some much-needed further research. As Spatz (2020) has suggested, perhaps it could be part of the answer to saving the lives of children throughout the pandemic and beyond?

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