Domperidone to stimulate lactation

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Breastmilk is the best food for all newborns, particularly for preterm infants.

In case the mother has an insufficient milk supply, the first intervention should be the optimization of breastfeeding or pumping technique, preferably under supervision of a lactation consultant. If this strategy is not sufficiently successful, prescribing domperidone to stimulate milk production can be considered.

The risk of side-effects in the child is negligible and the risk of heart arrhythmias as a result of prolongation of the QT interval in the mother is small, as long as domperidone is prescribed at low dosage (10 mg t.i.d).

In the absence of risk factors for QTc-prolongation, the mother does not need an ECG and her family doctor can safely prescribe domperidone.

The effect of the domperidone treatment should be evaluated after two weeks. In case of long-term prescription or higher dosage, it is advisable to make an ECG to exclude QTc-prolongation.

A 28-year old woman gave birth to a son at 24 1/7 weeks. She immediately started expressing milk, with a frequency of 7-8 times a day. Despite regular pumping with the right equipment, she did not succeed in producing more than 200 ml of breast milk per day. Intensification of the pumping regime and additional advice provided by the lactation consultant were not effective. Subsequently, she started taking domperidone 10 mg t.i.d., after which her production increased to 600 ml of breastmilk per day. She continued taking domperidone for the remainder of her breastfeeding period of 6 months.

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Breastfeeding is, without a doubt, the best food for all neonates, with advantages in the short and the long term for both mother and child.[1] In the Netherlands, 80% of all Dutch mothers initiate breastfeeding after birth. The past few years have shown a slight upward trend in the duration of the breastfeeding period, with almost half of all mothers still breastfeeding after 6 months.[2]

However, there are situations in which breastfeeding is impeded. This is particularly apparent when mother and child are separated due to hospitalization or when the child is not yet capable of drinking at the breast.[3]

In those situations, the advice is to pump breastmilk and then feed this to the child via bottle or gavage. Usually, the amount of pumped breastmilk is sufficient to fulfill the needs of the child.

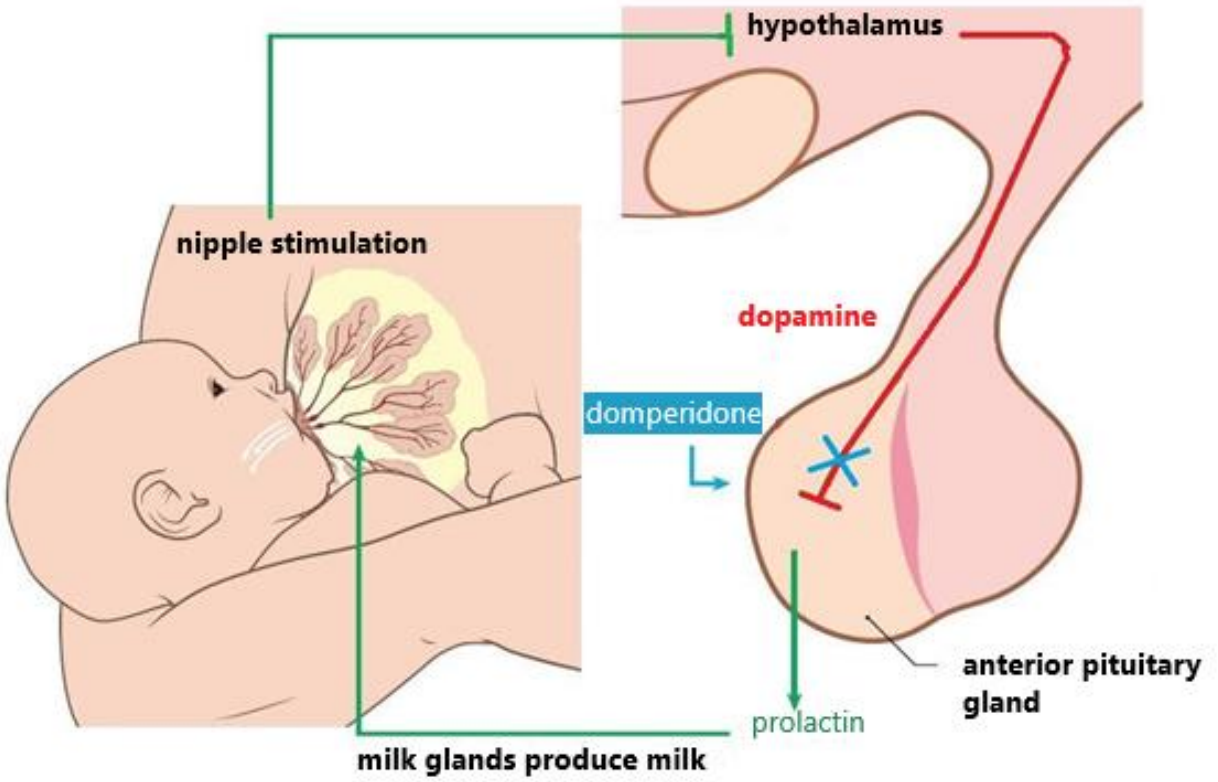

FIGURE 1 Physiology of the stimulation of milk production and operational mechanism of domperidone. A stimulus caused by suckling travels from the breast, through the spinal cord to the hypothalamus. Neurons from the spinal cord inhibit dopamine (DA) release from the arcuate nucleus. The decreased level of DA removes the inhibition that DA normally produces on lactotrophs through dopamine-D2-receptors in the anterior pituitary, leading to prolactin release. Domperidone blocks these dopamine receptors, resulting in increased prolactin release. Prolactin stimulates milk production in the breast. [Figure updated from original]

This does require good support, with attention for technique, frequency and lifestyle factors. The goal is to eventually have these children drinking from the breast themselves, as soon as they are capable of suckling. If despite these measures the milk production volume is insufficient, the first intervention will always be to consult a lactation consultant.

THE WORK OF THE LACTATION CONSULTANT

Most mother- and child health care facilities (hospitals, maternity assistance organizations and centers for youth and family) have a lactation consultant on staff who can be consulted for advice. Lactation consultants usually visit families in their homes, so mother and child do not have to travel. Parents and care providers can find the nearest lactation consultant on the website of the Dutch Association of Lactation Consultants.

Lactation care in the Netherlands is covered in supplementary health care insurance packages offered by most insurance companies.

In the exceptional cases in which milk production does not become abundant or diminishes and becomes insufficient, pharmacological support of milk production can be indicated. In practice, this situation particularly occurs in mothers of seriously premature infants. They have less physical contact with their child, experience more stress, and often have to deal with underlying morbidity and medication. Specifically for these neonates, the clinical importance of mother's milk is very high. Mother's milk has a preventive effect in premature newborns with respect to serious infections necrotizing enterocolitis, as well as an association with better neurocognitive development.[4-6]

Lactation consultants turn out to be very capable of determining the indication for pharmacological intervention and are bolstered in doing so by international breastfeeding organizations, but are not allowed to prescribe drugs.[7].

However, family doctors often indicate that they lack the information or the guidelines to adequately weigh the indication and possible contra-indications of domperidone. In this context, it is probably relevant that prescribing domperidone to stimulate lactation is off-label; moreover, family doctors can have reservations because of possible side-effects of this medication. In this article, we provide evidence for the prescription of domperidone to stimulate lactation. We hope family doctors will use this information in order to safely support treatment with domperidone. For this article, we used Dutch information sources that are often not available via PubMed, such as the magazine *Praktische Pediatrie*, NHG-standards, Teratology Information Service (TIS), the "*Farmacotherapeutisch Kompas"* and *Pharmaceutisch Weekblad*. In addition, we searched PubMed for relevant literature with the following search terms: 'premature infants', 'breastfeeding', 'breast pumping', 'inadequate milk supply', 'lactation failure', 'galactogogue', 'domperidone' and '(cardiac) side effects'.

EFFECT OF DOMPERIDONE ON LACTATION

Domperidone is a strong dopamine-D_2-receptorantagonist with a prokinetic effect. It was originally developed as an anti-emetic and is licensed in the Netherlands for both children and adults. Blockage of the inhibiting D_2-receptors in the anterior pituitary gland stimulates release of prolactin and subsequently the production of milk in the milk glands (figure 1). This side-effect is successfully employed in the medicinal stimulation of lactation, or 'galactagogue' effect. Domperidone stimulates milk production within 48 h after initiation of medication through an increase of the serum prolactin level, as was shown in 3 randomized double blind placebo controlled trials.[8-10] In 20 lactating women who used domperidone (10 to 20 mg 3 t.i.d.), the prolactin levels at the start of the trial were comparable to levels of lactating women who received placebo-treatment.[11] The prolactin concentration on day 5-10 after initiation of domperidone was statistically significantly higher compared to the placebo group. In the various studies, treatment duration differed considerably, but a significant increase of mother's milk production was seen in each trial. In the study in which the women were treated for 7 days, the placebo group exhibited an increase of 8 ml/day, compared to an increase of 50 ml/day in the domperidone group.[8] With a treatment duration of 10 days in another study, this increase was 63 ml/day in the placebo group versus 326 ml/day in the domperidone group, and with a duration of 14 days these increases were, respectively, 33 ml/days versus 196 ml/days.[9,12,13]

Use of domperidone as a 'breastfeeding treatment' was, therefore, recommended before in the magazine *Praktische Pediatrie* and by the Teratology Information Service (TIS), a department of the Netherlands Pharmacovigilance Centre Lareb.[14,15]

POTENTIAL SIDE-EFFECTS OF DOMPERIDONE

SIDE-EFFECTS WHEN DIRECTLY ADMINISTRATED TO INFANT

For many years, domperidone was prescribed on a large scale as a prokinetic in infants with serious gastroesophageal reflux complaints. Domperidone exhibits a high degree of protein binding (> 90%), has a high molecular weight and only passes the blood-brain barrier to a small degree. In *Farmacotherapeutisch Kompas* (Pharmacotherapeutic Compass; pharmaceuticals database published by the Dutch government, used by Dutch practitioners), caution is now called for in the direct administration of domperidone to children under one year old. In premature infants and other neonates, the metabolic functions and the blood-brain barrier are not yet fully developed, which may increase the risk of neurological and central side-effects. This specifically pertains to extrapyramidal disorders, convulsions, agitation and nervousness.

SIDE-EFFECTS OF EXPOSURE OF INFANT VIA HUMAN MILK

No serious side-effects of domperidone to stimulate lactation have been reported in the literature on either mother or infant. In various randomized controlled trials comparing domperidone (10 mg t.i.d.) to placebo, no significant side-effects were reported for a total of 44 lactating women.[8-10,12] Minor maternal side-effects were dry mouth and headache. In various studies, the amount of domperidone that reached the mother's milk was measured.[8,10,12] This enables calculation of the relative child dosage. The relative child dosages indicate the ratio between the estimated dose of medicine per kg body weight of the child that the child receives through the mother's milk and the dose the mothers gets (both in mg/kg/day). For domperidone this is low: 0,01-0,04% of the dose the mother consumes. Therefore, a very small amount transfers into the milk.[15] Furthermore, the oral biological availability is only about 15%, so even if domperidone reaches the baby via the milk, it still only becomes systemically available to a very limited degree.

With a maternal intake of 10 mg t.i.d. per os, a concentration of domperidone in the milk of 1,2 ng/ml and a milk intake of 150 ml/kg/day, the baby theoretically ingests a daily amount

of 0,2 µg/kg domperidone.[8,10,12] The exposure through this route, therefore, is thousands of times lower than the lowest dosage advised when using domperidone as a prokinetic in neonates (0,75 mg/kg/days in 3 or 4 doses).[14] Considering the extremely low dose via mother's milk, the risk of the child experiencing the described side-effects is negligible.

SIDE-EFFECTS ON MOTHER

A number of epidemiological patient-control-studies showed that use of domperidone is associated with a higher risk of ventricular tachyarrhythmia and sudden cardiac death, caused by prolongation of the QTc-interval through inhibition of a specific type of K^+-channel, the so-called hERG-channel.[16,17] Risk factors were age above 60 years, high dosages and interacting co-medication. Patients with a long-QT-syndrome also belong in the category of patients at risk. Relevant QTc-interval prolongation occurred in other studies in healthy volunteers at high doses, but never when using less than 80 mg per day.[18,19] Therefore, we consider this side-effect to be very rare in healthy young women with negative family histories for heart arrhythmias and no relevant co-medication.

STIMULATING LACTATION IN PRACTICE

LICENSING AND PRESENT GUIDELINES

Since domperidone is not formally licensed as a medication for the stimulation of mother's milk production, it is prescribed off-label. In the present NHG-guideline (guidelines published by the Dutch College of General Practitioners) 'Pregnancy and Puerperium' doctors are advised to only provide non-pharmaceutical support. Pharmacological stimulation of mother's milk production is advised against, because domperidone is not registered for this indication and because the clinical is supposedly not well established. On the other hand, Lareb (the Netherlands Pharmacovigilance Centre) does support treatment with domperidone to stimulate lactation.[15] The NHG-guideline however does not differentiate between healthy and sick neonates and does not take the health advantages of breastfeeding after premature birth into account.

In daily practice, lack of familiarity with the indication, the off-label status of domperidone, and the fear of possible side-effects, as well as the absence of support by the NHG guidelines, create unnecessary resistance against prescribing domperidone by the family doctor. This leads to dissatisfaction on the side of patients, who then turn to their pediatrician or gynecologist with their request for domperidone.

WHAT ARE POSSIBLE CONTRA_INDICATIONS IN THE MOTHER

Domperidone should not be prescribed to patients with a prolonged QTc-interval, a long-QT-syndrome or who are suspected of having these, use of strong CYP3A4-inhibitors (for instance ketoconazol or erythromycin), use of QT-prolonging medication, significant electrolyte disturbances (especially hypokalemia and hypomagnesaemia) and other risk factors for QT prolongation or torsade de pointes (for instance bradycardia, heart failure or cardiomyopathy).[20-22] Therefore mothers always need to be screened carefully for risk factors, such as a positive family history for prolonged QTc-interval, co-medication with prolongation of the QTc-interval as side-effect, or an electrolyte disturbance.

In case of risk factors, it is advised that an ecg be made in order to assess the QTc-before the mother starts taking domperidone.

If a normal ecg is available, which was made after the age of 18 years, it is not necessary to make a new ecg before initiation of treatment with domperidone. A QTc-time of > 500 ms is considered clinically relevant. However, when a patient starts taking elective medication, as a safety precaution an upper limit of 440 ms is used. In the absence of risk factors, it is not necessary to make an ecg.

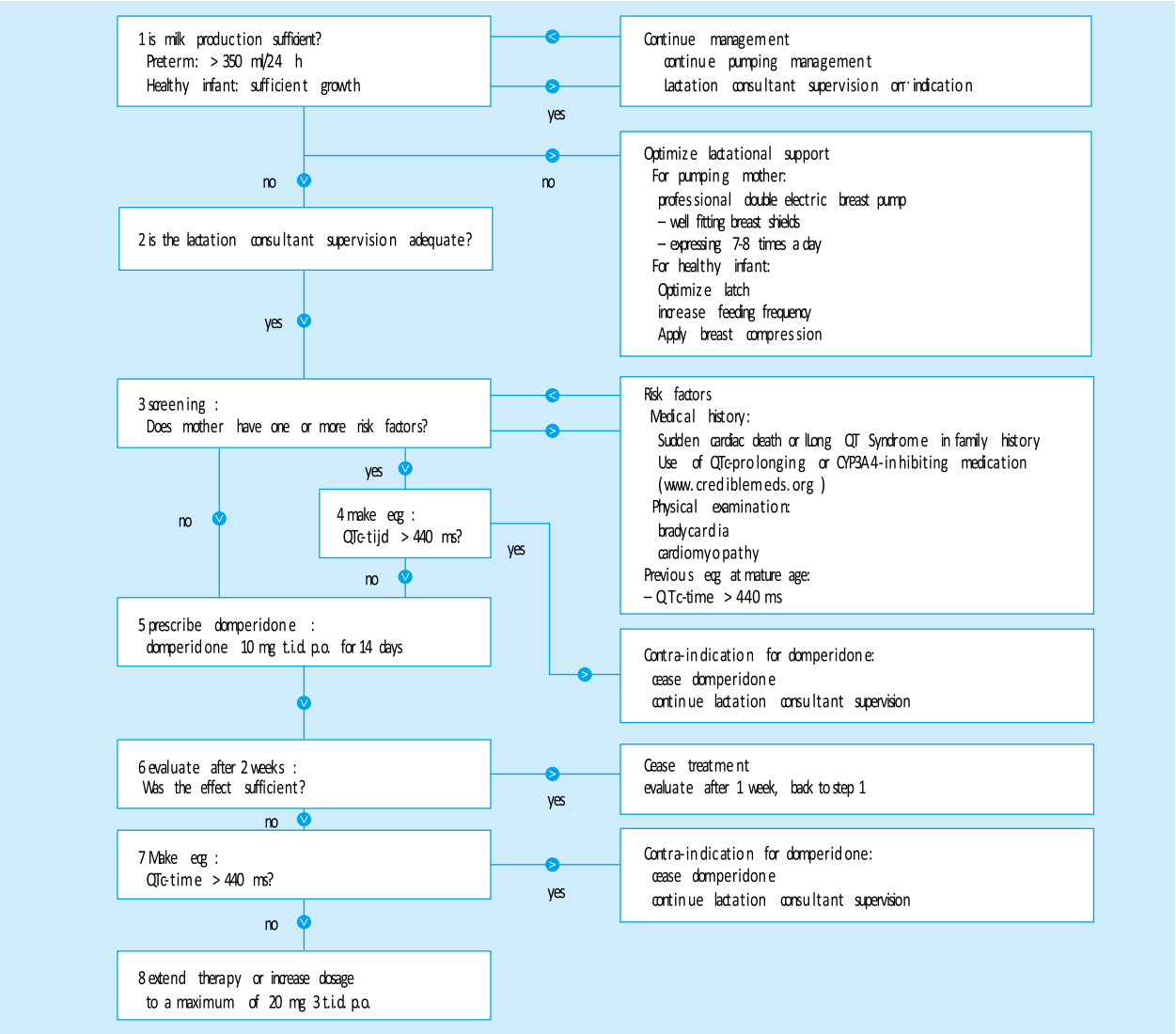

FIGURE 2 *Steps in case of insufficient milk production (QTc-time=QT-time corrected for heart frequency)*

STIMULATING LACTATION IN PRACTICE

WHO SHOULD PRESCRIBE THIS MEDICATION?

Because of the potential side-effects, it is recommended that domperidone to stimulate mother's milk production be prescribed by a doctor who is aware of the state of health and family history of the mother and who can provide follow-up. As pediatricians and neonatologists do not have the mother's data nor the treatment relationship with the mother, it is not preferable that these doctors should prescribe this medication. The same is to some extent true of the gynecologist, whose involvement is usually limited to pregnancy and childbed, whereas the indication for domperidone often develops after the maternity period.

PRACTICAL RECOMMENDATIONS

Figure 2 schematically shows the steps to be taken when mothers present with an insufficient milk supply. Primarily, lactation consultant care should be provided. When the indication for medicinal support is made, the family doctor should exclude risk factors. An ecg should be performed on indication. The starting dosage is 10 mg t.i.d. per os. After 14 days, the effect of the treatment should be evaluated. In case of insufficient effect, the mother should cease taking domperidone.

LEARNING POINTS

- **Human milk is the best nutrition for all neonates**
- **Lactation consultants can help increase the production of mother's milk**
- **Domperidone is an effective medication for stimulating mother's milk production.**
- **Though domperidone can lead to QTc-prolongation, the risk of side-effects is small in the population of lactating mothers.**
- **Domperidone can safely be prescribed by family doctors in low doses to women who have not exhibited risk factors for QTc-prolongation.**

There is little scientific evidence for a higher dosage. However, in practice we have some experience with higher dosing. When the treatment period is for a longer period or when the dosage exceeds 30 mg/day, we advise making an(other) ecg.

MOTHERS OF HEALTHY INFANTS

Mothers of healthy children can also experience insufficient milk production, through different causal mechanisms. These mothers are then compelled to feed their child formula. Optimal lactation consultant support should in these cases also be the first step and is usually sufficiently effective.

In all cases, attention should be given to the frequency of suckling and adequate latch technique. When this provides inadequate improvement, domperidone can increase the milk production of these mothers too, so that complimentary feeding can be completely or partially terminated. On the condition that the same risk factors have been excluded, there is no impediment to prescribing domperidone to mothers of healthy infants. This can also apply in cases of so-called induced lactation, when mother's milk is produced by a woman who did not herself carry the child in her womb, such as in case of adoption.

CONCLUSION

We advise family doctors to prescribe domperidone to mothers who despite adequate lactation consultant care still produce an insufficient amount of milk to feed their child. Risk factors for QT-interval prolongation should first be excluded.

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[Note: Recently, administration of domperidone to children under 12 years old is banned because of lack of efficacy for preventing nausea/vomiting. Use of domperidone as a prokinetic drug in children < 1year had been banned since 2014.]