Galactogogues: Medications That Induce Lactation

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Abstract
Galactogogues are medications that aid in initiating and maintaining adequate milk production. Most exert their pharmacologic effects through interactions with dopamine receptors, resulting in increased prolactin levels and thereby augmenting milk supply. Metoclopramide remains the galactogogue of choice due to its documented record of efficacy and safety in women and infants. Domperidone crosses the blood brain barrier and into the breast milk to a lesser extent than metoclopramide, decreasing the risk of toxicity to both mother and infant possibly making it an attractive alternative. Traditional antipsychotics, sulpiride and chlorpromazine, have been evaluated, but adverse events limit their use. Human growth hormone, thyrotrophin-releasing hormone, and oxytocin have also been studied. Finally, a natural product, fenugreek, has been purported to be effective in anecdotal reports. Use of this agent may be warranted after considering risks versus benefits. J Hum Lact. 18(3):274-279.

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The production of breast milk is controlled by an interplay of various hormones, with prolactin being the predominant hormone involved. The maturation of breast tissue, resulting in milk production, is controlled by many other factors besides prolactin, including estrogen, progesterone, insulin, growth hormone, cortisol, thyroxine, and human placental lactogen. During pregnancy, high levels of estrogen and progesterone inhibit the effects of prolactin on breast milk production. A dramatic reduction in progesterone following delivery triggers lactation. Nipple stimulation, via suckling or manual stimulation, initiates release of prolactin from the anterior pituitary and oxytocin from the posterior pituitary gland. Other sensory pathways may affect the release of oxytocin beyond nipple stimulation. The release of prolactin from the anterior pituitary stimulates the production and secretion of breast milk, while the release of oxytocin from the posterior pituitary aids in the contraction of myoepithelial cells within the breast, resulting in milk letdown. The release and production of prolactin is dependent on the inhibition of a factor known as prolactin inhibitor factor, which is produced by the hypothalamus, and dopamine-releasing neurons. The activation of dopamine receptors on prolactin-secreting cells inhibits the release of prolactin. Prolactin does regulate the volume of milk produced; however, once lactation is established, infant demand drives the process. In the absence of suckling, lactation ceases in 2 to 3 weeks.

Galactogogues
A variety of prescription medications and natural products have been used as galactogogues—medications that induce lactation. Galactogogues are useful for women who are unable to produce breast milk on their own due to infant prematurity, illness of the mother or child, adoption, or surrogate motherhood. The medications used to induce lactation generally exert their
effects through antagonism of the dopamine receptor, which results in a subsequent increase in prolactin release. Prior to use of these medications for the promotion of lactation, other factors that may result in insufficient milk supply should be corrected, including correcting the infants’ latch to the nipple to maximize milk intake, correcting suckling problems using breast compression, and expressing milk after feedings to increase supply.2

Metoclopramide

The vast majority of published clinical data evaluating the use of drug therapy for breast milk production focuses on metoclopramide, which promotes lactation by antagonizing the release of dopamine in the central nervous system. This drug can cause extrapyramidal side effects, which may include tremor, bradykinesia, (slow movements) and other dystonic reactions.3 Metoclopramide stimulates the upper gastrointestinal tract through a similar mechanism in the gastrointestinal tract. It is indicated for the symptomatic treatment of gastroesophageal reflux disease, diabetic gastroparesis, and prevention and treatment of nausea and vomiting associated with chemotherapy and postsurgical situations. Usual dosing of metoclopramide in neonates for gastroesophageal reflux disease ranges from 0.4 to 0.8 mg/kg/day in 4 divided doses.4

Lewis and colleagues evaluated the extent to which metoclopramide passed into breast milk in 10 women.5 All women were breastfeeding their newborns 7 to 10 days after delivery, prior to receiving a single 10-mg oral dose of metoclopramide. Two hours after receiving this dose, blood and milk samples revealed mean concentrations of metoclopramide of 69 ± 30 ng/mL in maternal plasma and 126 ± 42 ng/mL in breast milk. Assuming a total daily milk intake of 1 L, the authors concluded that the average intake of metoclopramide by an infant would be less than 0.13 mg/kg or approximately 0.045 mg/kg/day for an average full-term newborn, which is well below the therapeutic dose used in preterm and term newborns. In addition, metoclopramide therapy was not observed to affect the amounts of prolactin, thyroid-stimulating hormone (TSH), or thyroxine in the infant.5 Kauppila et al reported a dose response relationship between improved lactation and metoclopramide 5, 10, or 15 mg 3 times daily in 37 mothers who had deemed their breast milk production insufficient during the initial 2 months after delivery.7 Daily doses of 30 and 45 mg of metoclopramide resulted in significant increases in serum prolactin levels and milk yield, with the 45 mg daily dose producing a faster onset of effect.

Following the documentation of this relationship between metoclopramide administration and improved lactation, a study was undertaken to evaluate the effects of metoclopramide therapy 10 mg orally 3 times daily for 10 days in 32 women with total or partial lactation failure.8 Total lactation failure (12 cases) was defined as either a total absence of milk flow or secretion of just a few drops of breast milk following suckling for at least 7 days. Partial lactation failure (20 cases) was defined as either inadequate milk output or the need for supplemental feedings to sustain growth. Response to therapy was evaluated after 5 and 10 days. All positive responses to metoclopramide were followed for a total of 8 weeks. Eight of the 12 complete failure cases responded to therapy with lactation beginning after a mean period of 3.4 days. All responders maintained improved lactation throughout the 8-week follow-up period. However, supplementary feedings were needed to maintain growth. Of the 20 mothers with partial failure, all responded with an increase in milk flow after a mean period of 3.4 days. The amount of supplementary milk feeds at baseline was 270 ± 37 mL/day, which was reduced to 153 ± 39 mL/day after 8 weeks. Seven of the 20 infants had supplemental feedings eliminated completely within a period of 5 to 11 days after initiation of metoclopramide. No adverse effects were noted in the study with regard to metoclopramide therapy.

Metoclopramide has also been administered to the intended mother of a surrogate pregnancy.9 A 27-year-old woman, with a congenital absence of the uterus, was treated with oral metoclopramide 10 mg 3 times daily to induce lactation prior to reception of her newborn through a surrogate mother. Treatment was initiated when the surrogate was 28 weeks pregnant and continued until 1 week prior to the expected delivery date. Therapy was well tolerated and lactation was successfully induced; however, insufficient quantities of breast milk were produced to breastfeed exclusively. This same approach has been documented to be successful in a case of an adoptive mother who wished to breastfeed her adoptive child.10 This case involved a 34-year-old adoptive mother who began pumping her breast every 3 to 4 hours and took 10 mg of metoclopramide 3 times
daily to increase her prolactin level. Use of metoclopramide, with nasal oxytocin (a product no longer available in the United States) to promote letdown, resulted in successful induction of lactation.

Ehrenkranz and Ackerman reported the effective use of metoclopramide by mothers of premature infants. Reduction in milk production is commonly observed in mothers of premature infants when lactation has been maintained primarily by milk expression without infant suckling. Twenty-three mothers of premature infants were administered metoclopramide 10 mg orally every 8 hours for 7 days with a subsequent taper over 2 days. Milk production significantly increased between the first and seventh days, from a baseline of 93 ± 18 mL/day (P < .001) in 17 women, for whom complete milk production records were available. Maternal side effects observed during therapy included diarrhea and nervousness. No adverse effects were observed in the breastfed infants. A significant increase in serum prolactin levels was also noted in women for whom baseline and posttreatment levels were available (18 ± 3 ng/mL to 122 ± 22 ng/mL; P < .001).

Budd et al described a case of a premature infant admitted to the hospital due to severe hypernatremic dehydration. The mother had reduced milk production and was initiated on metoclopramide 10 mg orally 3 times daily. In addition, prematurity and inadequate milk flow were operating together to increase the sodium concentration of the milk. Treatment with metoclopramide resulted in an increase in prolactin concentrations and subsequent improvement in milk flow and a reduction in milk sodium concentration. A similar positive result with metoclopramide therapy was reported by Toppare et al in 32 women with lactational insufficiency and babies 10 to 120 days of age (16 preterm infants and 16 full-term) who had failed to thrive. Metoclopramide therapy resulted in a significant (P < .05) increase of 82.5% in daily milk production and a 34% increase in prolactin concentration, with minimal side effects reported in 3 mothers and none in the infants.

The use of metoclopramide, in a dose of 10 mg orally 3 times daily, has been documented to be an effective and safe therapy for the initiation and maintenance of lactation throughout the biomedical literature. The therapeutic usefulness of this medication as a galactogogue has been observed in a variety of situations, including prematurity, illness of the mother or child, adoption, and surrogate motherhood.

**Domperidone**

Domperidone is also a dopamine antagonist that is available outside the United States for the treatment of chronic postprandial dyspepsia, reflux esophagitis, and emesis. The usual oral dosing range varies from 10 mg 3 times daily to 40 mg 4 times daily dependent upon indication. Administration of domperidone results in increases of mean serum prolactin levels in normal women from 8 to 111 ng/mL following a single 20 mg dose. Doses used for induction and maintenance of lactation range from 10 to 30 mg 3 times daily. Domperidone exerts its pharmacologic effects in the periphery rather than centrally like metoclopramide. Domperidone is less lipid soluble, has a larger molecular weight, and has lower protein binding as compared with metoclopramide. These characteristics contribute to the limited amount of the drug that crosses the blood-brain barrier, possibly reducing extrapyramidal side effects.

In comparison to sulpiride and metoclopramide, domperidone crosses less freely into breast milk as well. A case report, involving 2 mothers of preterm infants, provides pharmacokinetic data on the excretion of domperidone into breast milk. The dose of domperidone administered 10 mg every 8 hours, revealed that passage of domperidone into breast milk occurred in smaller amounts relative to therapeutic dosages of metoclopramide or sulpiride (M = 125.7 ng/mL, S = 970 ng/mL, and D = 2.6 ng/mL).

In a recent, randomized, double-blind, placebo-controlled study, 20 women were assigned to receive either domperidone (11 women) 10 mg orally 3 times daily or placebo (9 women) for 7 days. In the final analysis, 4 women were excluded, 3 had incomplete milk records, and 1 infant died of neonatal complications. As compared to baseline, the mean increase in milk yield from days 2 to 7 was significantly higher (P < .05) in the domperidone group (50 ± 29 mL) as compared to the placebo group (8 ± 40 mL), even though the domperidone group had a significantly higher milk volume at baseline. In addition, serum prolactin levels were significantly increased by domperidone therapy (P = .008). The results of this trial confirm that domperidone is an effective and safe method of inducing lactation during short-term use. Domperidone may be an alternative to metoclopramide therapy if it is available for use. However, studies are needed to assess the long-term effects of domperidone. Domperidone is the only galactogogue available that has been scientifically eval-
uated through a randomized, double-blind, placebo-controlled study.

**Sulpiride**

Sulpiride is a typical antipsychotic, also not available within the United States, that serves as a galactogogue by increasing hypothalamic prolactin-releasing hormone. The typical dosage for initiation of lactation is 50 mg 2 to 3 times daily. Maternal side effects include extrapyramidal effects such as tremors, bradykinesia, or acute dystonic reactions, and possible endocrinological concerns such as weight gain. The use of sulpiride to increase milk production has been evaluated in 2 studies. Ylikorkala et al administered sulpiride 50 mg orally 3 times daily or placebo to 24 women who believed their milk yields to be insufficient during the initial 4 months after delivery. Therapy was continued for a 2-week period. In addition, supplemental buccal oxytocin was administered to some patients. One woman in the sulpiride group and 3 in the placebo group discontinued therapy owing to lack of effect. Daily milk yield was significantly greater with sulpiride therapy versus placebo both at 1 week (628 ± 51 mL vs. 440 ± 68 mL) and 2 weeks (684 ± 67 mL vs. 423 ± 60 mL) of treatment ($P < .05$). Higher serum prolactin concentrations were also noted in women receiving sulpiride therapy. The additional use of oxytocin resulted in no effect on lactation in those mothers whose infants were able to suck normally.

In another study, 96 women were administered 50 mg of sulpiride twice daily or placebo for 4 days from the third postpartum day. Forty-two were primiparous women, and 54 were multiparous women. In the primiparous women, both sulpiride and placebo-treated women experienced an increase in milk yield from the first to fifth postpartum days. Reported breast milk volumes were significantly higher on the fourth and fifth days in the sulpiride group versus control ($P < .01$). There was a mean total milk yield increase of 49.9% for the third to fifth postpartum days when comparing the control group with the sulpiride group. For multiparous mothers, a significant difference in total milk yield was not observed between control and sulpiride groups. The significant difference in total milk yield in primiparous mothers not observed in multiparous mothers may be due to primiparous mothers having smaller nipples and not being accustomed to nursing. This situation makes suckling more difficult for the nursing infant initially, resulting in reduced prolactin secretion.

**Chlorpromazine**

Chlorpromazine, another typical antipsychotic, has also been used as a galactogogue. In case reports, a dose of 25 mg orally 3 times daily for 1 week has been used successfully to promote lactation. Chlorpromazine is conformationally similar to the dopamine molecule and has the ability to bind and block the dopamine receptor, resulting in increased prolactin levels. The use of typical antipsychotics, such as sulpiride or chlorpromazine, for the promotion of lactation has been documented; however, use of these agents is limited owing to the possibility of developing adverse effects, including extrapyramidal reactions and weight gain.

**Growth Hormone**

The exact mechanism of action by which human growth hormone may stimulate lactation remains unknown. The development of a controlled trial to evaluate the effects of human growth hormone on lactation was based on animal data observed in cows. In this randomized, double-blind, placebo-controlled trial, 16 healthy, lactating women received either recombinant human growth hormone in a dose of 0.1 IU/kg/day subcutaneously, or placebo injection, on days 3 to 9 of a 10-day study period. At baseline, milk production volumes were similar in both groups. After 7 days of therapy, there was a significant increase ($P < .02$) in milk volume in the human growth hormone–treated group (18.5 ± 1.5%) as compared with the placebo-treated group (11.6 ± 2.0%). No major changes in milk constituents and no adverse effects were observed in the mothers. The use of this drug as a galactogogue is limited. Studies evaluating the use of human growth hormone in women with actual lactational insufficiency are lacking, as is safety data in breastfeeding infants.

**Thyrotrophin-Releasing Hormone**

Thyrotrophin-releasing hormone (TRH) is available in the United States as a diagnostic agent in the assessment of thyroid function. It is structurally similar to naturally occurring TRH, which increases the release of both TSH and prolactin. Peters et al evaluated the use of TRH as a galactogogue in 19 women with inadequate lactation, defined as less than 50% of normal milk yield, on the fifth day postpartum. In a random fashion, 10 of the women received a nasal spray formulation of TRH and 9 received a 0.9% sodium chloride spray for 10 days starting on day 6 postpartum. One spray, equivalent to
1 mg of TRH, was administered 4 times daily at prespecified times. At the end of the initial 10-day period, milk production was significantly increased in the TRH group from a mean of 142 gm/day to 253 gm/day ($P = .014$). Seven women in the TRH group requested further treatment for an additional 10-day period. Continued therapy resulted in a further increase in milk yield, up to 424.3 gm/day. Administration of long-term high-dose (40 mg) oral TRH administration has been associated with the development of hyperthyroidism in women administered the medication, but this effect was not observed in patients in this trial. Use of TRH for initiation and maintenance of lactation is not commonly done in clinical practice.

Oxytocin

Although used commonly in the past in the United States, oxytocin is no longer on the market. Oxytocin is typically used to promote milk letdown; however, it has been evaluated to enhance the onset of lactation among 8 mothers of premature infants. Subjects were given a spray bottle containing either oxytocin 40 U/mL or a blank solution and were instructed to administer 1 spray in each nostril (total dose of 3 U oxytocin) prior to pumping milk. The effect of the spray on milk production was highly significant, resulting in a 3- to 5-fold increase in milk production in primiparas and a 2-fold increase in multiparas. No significant change in composition of breast milk was noted.

Fenugreek

Fenugreek is a natural product that is a member of the pea family. It has been used for a variety of indications, including treatment of cough, bronchitis, sore throats, and menstrual pain. Anecdotal reports of the successful use of fenugreek as a galactagogue have been documented as far back as 1945. However, formal published clinical data are lacking. A specific mechanism of action is unknown; however, it has been theorized that fenugreek may affect breast milk production by stimulating sweat production, and the breast is a modified sweat gland. In a clinical practice setting, Huggins describes the anecdotal use of the herb in at least 1200 women. Generally, all the women who consumed fenugreek reported an increase in milk production within 24 to 72 hours after initiation of therapy. Discontinuation of the herb can occur after milk production is stimulated to an appropriate level and maintained as long as breast stimulation and emptying continue. The recommended dose of fenugreek for use as a galactagogue is 2 to 3 capsules 3 times daily. The amount of fenugreek in each capsule may vary from batch to batch, as there are no standardization requirements for herbal products at present. Reported adverse events are rare and may include a maple-like odor to urine and sweat, diarrhea, and aggravation of asthmatic symptoms. Use of fenugreek during pregnancy is contraindicated because of its uterostimulant effects.

A variety of other natural products have anecdotally been reported to increase breast milk production, including anise, basil, blessed thistle, caraway, chasteberry, cotton, fennel, goat’s rue, luffa, squawvine, and verbena.

Specific published clinical data are lacking supporting the use of these natural products for the promotion of lactation.

Conclusion

Galactogogues have been used in a variety of settings to promote and maintain lactation, including prematurity, failure to thrive, adoption, and surrogate motherhood. Prior to use of these medications, correction of modifiable factors, which may result in insufficient milk intake in the newborn, should be undertaken. The majority of published clinical data involves the use of metoclopramide to increase prolactin concentrations and milk yield. Therefore, metoclopramide 10 mg orally 3 times daily for approximately 1 to 2 weeks should be considered the therapy of choice for the initiation and maintenance of lactation; improvement in milk production generally occurs in 2 to 5 days. Both mothers and infants should be observed for extrapyramidal side effects. Domperidone, another dopamine receptor antagonist, crosses into the breast milk and blood-brain barrier to a lesser degree than metoclopramide and may be an alternative option if available. Sulpiride and chlorpromazine are typical antipsychotics that have been documented to be effective as galactogogues. However, the possibility of adverse effects such as extrapyramidal reactions and weight gain limit their use. Human growth hormone and thyrotrophin-releasing hormone are other agents that have been utilized, but these agents have very limited clinical experience behind them. Oxytocin, although widely used in the past, has limited scientific data as a galactagogue and is no longer available in the US market. The data involving fenugreek are completely anec-
dotal in nature. Administration of fenugreek in situations where lactational insufficiency is a problem should be done only after weighing the risks versus benefits.

References


Resumen

Los galactólogos son medicinas que ayudan a la iniciación y el mantenimiento de la producción adecuada de leche. Muchos se oponen a reconocer sus efectos farmacológicos mediados por interacciones con los receptores dopamínicos, que resultan en aumento en los niveles de prolactina y así se incrementa la producción de leche. La Metroclopramida sigue siendo el galactólogo de preferencia debido a su eficiencia y seguridad tanto para la madre como para el niño, posiblemente convirtiéndose en una alternativa atractiva. Antisicóticos tradicionales, sulpride y chlorpromazina se han evaluado, pero algunos eventos adversos han limitado su uso. La hormona del crecimiento, la hormona estimulante de la tiroides y la oxitocina se han estudiado al mismo tiempo. Finalmente, un producto natural como el fenugreek (fenugreco), ha mostrado efectividad en reportes anecdóticos. El uso de este producto se garantiza luego de considerar cuidadosamente los riesgos y beneficios.