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Review

A Critical Review of Pharmaceutical Galactagogues

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ABSTRACT

Use of plant and drug products to enhance lactation is widespread, and numerous papers have been published in the medical literature claiming efficacy for various products. This paper will review and evaluate the published literature on the most widely used pharmaceuticals that are used as galactagogues. Breastfeeding physiology is reviewed with the aim of creating a framework for understanding galactagogue pharmacology. Published articles were selected and evaluated using the principles of evidence-based medicine, and were also evaluated using the principles of good lactation management. Only three studies on oxytocin and seven studies on dopamine antagonists were found to be useful. Oxytocin is probably not useful as a galactagogue, except possibly in rare circumstances of tetraplegic mothers. Dopamine antagonists appear not to enhance milk supply if mothers are given good lactation support and employ these practices. The safety of the dopamine antagonists has not been adequately evaluated, so their use should be avoided unless other measures have failed.

INTRODUCTION

GALACTAGOGUES ARE DRUGS or other substances that are purported to enhance milk production. Numerous botanicals have been used in folk medicine for countless years to increase milk supply. More recently, synthetic pharmaceuticals have been used as galactagogues in conventional Western medicine. This paper evaluates the clinical studies that have been performed on the most commonly used pharmaceutical galactagogues. To understand how galactagogues might be useful clinically, highlights of the processes of milk production are reviewed.

LACTOGENESIS AND MILK PRODUCTION

Milk production by some alveolar cells begins between 10 and 22 gestational weeks, during what has been called initiation phase or lactogenesis I.[1] A small amount of milk is produced immediately after birth, 37 to 169 mL of colostrum during the first 48 hours.[2] It is not until the drop in the mother's serum progesterone after delivery that the milk production occurs between 24 and 102 hours postpartum. This has been called lactogenesis II.[3]

By day 5 postpartum, women can produce 500 to 750 mL of milk daily, and by day 14 post-

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partum, from 700 to1000 mL daily.[4] Mothers of twins or triplets, or those who practice tandem nursing of a newborn and an older sibling can produce over 2 L of milk daily,[5–7] illustrating how normal physiological mechanisms can adapt milk production to the increased needs of nursing infants over a wide range.

Prolactin

Prolactin, which is secreted by the anterior pituitary gland in response to nipple stimulation, is under inhibitory control from the hypothalamus mediated in part by dopamine.[8,9] The serum prolactin concentration increases during pregnancy from 10 μg/L in nonpregnant women to 200 μg/L at term. However, as noted above, prolactin is prevented from exerting its effect on milk secretion by elevated levels of progesterone.[3,10] After delivering, nonbreastfeeding mothers' basal prolactin return to prepregnant levels at 2 to 3 weeks postpartum.[11] In women who are nursing, basal serum prolactin remains elevated and spikes higher with nipple stimulation. One study found that the basal serum prolactin in lactating women averaged 119 μg/L during the first month postpartum and declined to 59 μg/L at 6 months postpartum, which is still higher than in nonpostpartum women. Serum prolactin levels after stimulation by infant suckling are about double that of basal prolactin: 286 μg/L at 1 month and 91 μg/L at 6 months.[12] In another study, the postsuckling prolactin increase doubled when two infants were nursed simultaneously, suggesting that the amount of prolactin released might be related to the degree of nipple stimulation.[11]

One study of 20 mothers measured serum prolactin at 10, 20, 30, 45, 60, 90, and 120 minutes after the beginning of nursing or pumping. The increase of serum prolactin among 11 women deemed "good breastfeeders" (mean 80 $\pm$ 3 g [SEM] of milk after sucking for 10 minutes), was similar to 9 "poor breastfeeders" (mean 46 $\pm$ 4 g [SEM] of milk) at days 5 to 6 postpartum. Another six women who expressed a mean of 86 g of milk with a Humalactor electric pump, which applies only negative pressure and provides little nipple stimulation, did not experience a measurable increase of serum prolactin during this same time interval.[13]

In another study, an increase in serum prolactin occurred with the bilateral White River electric pump that was greater than the increase from nursing the infant in the same mothers. The increase was smaller when the mothers used hand expression or a battery pump. The authors did not measure the volume extracted by the infant, but the electric pump extracted almost twice as much as hand expression.[14]

A study of 11 nursing mothers did not find any relationship between basal or sucking-stimulated serum prolactin concentrations or milk prolactin concentration and the short-term rate of milk synthesis as measured by the change in breast volume between feeds. The authors concluded that milk production is not directly controlled by basal or postsucking serum prolactin. They noted that prolactin may have a permissive effect on milk synthesis, but autocrine factors have a more important role in regulation of milk production.[12] These studies all emphasize the lack of direct correlation between basal or peak serum prolactin and milk production.

Oxytocin

When the infant suckles at the breast, sensory nerves in the areolae are stimulated. The afferent impulses are transmitted to the hypothalamus, leading to release of oxytocin from the posterior pituitary.[11] In many lactating women, there is an increase of oxytocin even before nursing the infant with an initial let-down, and a second release after the infant sucks several times, with an abrupt decrease approximately 20 minutes after the beginning of sucking. The effects of oxytocin are brief, allowing the breast to empty.[15]

Oxytocin release is inhibited by catecholamines that are produced if the mother is stressed or has pain.[16] Preventing and solving breastfeeding problems that cause pain and stress is essential to breastfeeding success.[17]

Feedback inhibitor of lactation

Animal studies have identified the functions of a low molecular weight glycoprotein synthesized in the mammary gland and secreted

into milk called feedback inhibitor of lactation (FIL). FIL appears to account for the effect of breast emptying on milk production. It acts rapidly (minutes) by reversible blockade of protein synthesis of the mammary secretory cells. As FIL accumulates in the alveoli between feedings, it blocks protein secretion. When the breast is emptied, the blockade stops, and the mammary cell resumes production of protein and lactose, which is responsible for the volume of milk. Over a time period of days of not emptying the breast, accumulation of milk and the continued presence of FIL also reduces the number secretory cell surface receptors for prolactin. FIL might have an effect on cell activity and eventually, decrease the number of secretory cells.[18,19]

Human data appear to be consistent with these animal findings. During lactogenesis II, the first 4 weeks of breastfeeding, the amount of milk produced is related to the number of feedings. During established lactation, this effect is less evident, but milk production can be increased by increasing the number of feeds or by emptying the breast after feeding. This supports the concept that infants can regulate the volume they need by both mechanisms: nursing more frequently or emptying the breast more completely.[5,6]

In the study of 11 nursing mothers cited above, the number of feedings was maintained for the first 6 months at 9.6 breasts/day at 1 month to 9.9 breasts/day at 6 months, although the duration of each breastfeed was nonsignificantly shorter at 1 and 6 months, 30.3 to 25 minutes, respectively (a "breast" is feeding from one breast; nursing from each breast in one feeding is considered two breasts).[12] Milk production was stable during the first 6 months when corrected for individual variations, with mothers who nursed more frequently producing more milk. The mean short-term rate of milk synthesis remained constant throughout the 6 months at 20–23 mL/hour. Milk production was very different between breasts for individual women and for individual nursing episodes, demonstrating that milk synthesis is controlled independently in each breast. This study did not find any relationship between the amount of milk removed and the rate of milk synthesis after that feed.

Summary

Prolactin appears to play a permissive role in milk production, but there is little or no correlation between serum prolactin levels and the amount of milk produced, particularly during established lactation. Frequent milk removal from the breast is critical in maintaining milk supply because it minimizes the effects of local substances that inhibit milk production.

Lactation has a robust physiology to sustain it. Nevertheless, when practices related to delivery and infant feeding interfere with factors that support the physiology (e.g., delayed initiation of breastfeeding, separation, scheduled feeding, and use of glucose water or formula feeding), some women have difficulty producing enough milk for their infants.[17,20]

STUDIES ON GALACTAGOGUES

To adequately evaluate studies on galactagogues, two types of factors must be taken into account. First, the principles of evidence-based medicine, such as blinding, randomization, and placebo control, should have been followed. Important factors to be considered in patient selection are whether the mothers were breastfeeding their infants or pumping their milk, if their infants were full-term or preterm, the age of the infants, whether the mothers received instruction on breastfeeding technique, and whether they had previous experience with breastfeeding, either successful or unsuccessful. Second, the principles of good lactation management should have been followed in the studies. Many of the studies on galactagogues were performed before these management principles were fully elucidated and fall short for this reason.

Selection and evaluation criteria

Studies on the use of a galactagogue that measured an increase in milk supply or infant weight gain were selected for evaluation. Those that were randomized, placebo controlled, and blinded were primarily used to evaluate the efficacy of galactagogues. However, some studies of note, because of their otherwise good design or their wide citation, are also discussed.

Studies that only measured changes in serum prolactin levels were not included because of the poor correlation between serum prolactin and milk production noted above, which was borne out in several of the galactagogue studies.

Enrollment criteria into studies were quite variable among studies. Some studies enrolled patients without regard to previous lactation experience or current lactation problems. Other studies used more narrow criteria, such as mothers of preterm infants or mothers who had a Cesarean section, while others enrolled mothers in whom good lactation management had failed to sufficiently increase milk supply. The time postpartum also varied among the studies, which is important because of the differences in the role and serum levels of prolactin in the various stages of lactation. Although the variability in selection criteria do not necessarily constitute shortcomings, it makes it difficult to compare studies or combine study results. Results from one maternal population may not be applicable to others.

Lactation management factors that were noted in the studies are whether the mothers were breastfeeding, pumping, and if so, what type of pump, or manually expressing milk. Whether they had prior breastfeeding history and whether they received instruction on lactation and proper nursing technique were also noted.

The age of the infants and the number of feedings per day is also important. In some studies newborns were nursed only every 4 to 6 hours, which is insufficient for optimum establishment of lactation. Newborns should receive least 8 to 12 feeds per 24 hours.[20,21] In other studies, infants received supplemental feedings, but the papers often did not report which supplement, how much or how supplements were given. Supplementation could decrease the mother's ability to establish her milk supply and thereby affect the study results. Other factors to consider in evaluating studies are the absolute increase in milk production and the final volume of milk rather than the percentage of increase in milk production as well as the success of the mother in establishing lactation. A large percentage increase of a small starting volume may be of little importance clinically. Finally, some studies measured only short-term increases in milk production and not long-term lactation success as their endpoint. These short-term differences might not be meaningful in overall breastfeeding success.

OXYTOCIN ENHANCEMENT

An early randomized, placebo-controlled trial used oxytocin nasal spray in the mothers of newborns, but lactation management fell far short of what is considered acceptable today, with a glucose feeding being given at 12 hours and breastfeeding not initiated until 20 hours postpartum. The study found that the spray might be useful in decreasing breast engorgement slightly in the mothers of full-term infants, but no difference was found in the average infant weight loss between birth and day 4 in the oxytocin and placebo groups.[22]

Two similar well-designed trials studied oxytocin nasal spray in mothers of preterm newborns who were pumping milk for their infants. The first studied mothers of infants born before 38 weeks and used a total of 3 units of intranasal oxytocin (Syntocinon–Sandoz, Holzkirchen, Germany, 40 units/mL) before pumping each breast for 10 minutes with an Egnell breast pump four times daily.[23] The paper did not report giving the mothers any instructions in lactation technique. Among primiparous mothers, total milk production from day 2 to 5 postpartum was 1964 mL in those who used oxytocin and 510 mL in those who received placebo spray. Because of the large and statistically significant effect of oxytocin among primiparous women, the trial was stopped after only 12 mothers of the planned 56 had been studied: 8 primiparous and 4 multiparous. No statistically significant difference was found between oxytocin and placebo among the four multiparous women who were attempting to breastfeed for the first time.

More recently, 51 mothers who delivered an infant of less than 35 weeks gestation were studied.[24] Twenty-seven mothers used 4 units of intranasal oxytocin (Syntocinon–Novartis, East Hanover, NJ, 40 units/mL), which is the manufacturer's recommended dosage, and 24

mothers received an identical placebo spray before pumping with an Egnell Ameda Elite breast pump (Hollister, Inc., Libertyville, IL). All mothers were given instructions on using hand massage before pumping and advised to pump every 3 hours by postpartum staff. Mothers were visited by the study nurse daily and had access to her at other times. No statistical difference in total milk production over the first 5 days postpartum was found between mothers who received oxytocin (median 667 mL) and placebo (median 530 mL), although women receiving oxytocin produced slightly more milk on day 2 of the study. Parity had no effect in this study. A survey administered to mothers in the study found no difference in their overall positive opinion of the efficacy of the spray whether they received oxytocin or placebo. Several factors might explain the differences in findings between the studies. Because of the great interpatient variability in milk production documented in the much larger recent study and the small number of patients in the first study, the finding in the earlier study may have been due to chance. A 50% higher dose of oxytocin was used in the first study, which may have caused a greater effect. Another plausible explanation is the good lactation support given to mothers in the recent larger study that seemed to be lacking in the early study.

Negative clinical experience with oxytocin nasal spray and its subsequent low use apparently preceded the most recent study, since the manufacturer discontinued marketing oxytocin nasal spray in most countries several years ago. However, two case reports indicate that oxytocin nasal spray may facilitate letdown in tetraplegic women who have lost the neuronal connection between the nipple and the hypothalamus.[25]

PROLACTIN ENHANCEMENT

Pharmaceutical galactagogues used today are dopamine antagonists. They increase serum prolactin by counteracting the inhibitory influence of dopamine on prolactin secretion. Although older agents such as chlorpromazine have been used,[26] the drugs that are now most widely used are metoclopramide, domperidone, and sulpiride. Because the first reliable international reference standard for prolactin assay was not available until 1988,[27] serum prolactin values reported before this time do not necessarily correlate with those in later reports.

Metoclopramide

Metoclopramide was originally marketed in Europe as an antipsychotic and later in the United States as a gastrokinetic agent. Its use as a galactagogue was first reported in 1975[28] in a letter to the editor, and it was first systematically studied in 1979.[29] Metoclopramide is by far the best studied galactagogue, with 14 clinical trials having been published.[26,29–41] in addition to numerous case reports and case series.

Most of the studies have designs that would not be considered valid using today's evidence-based medicine standards. Many of the studies had no placebo control;[26,30,31,34,36,39,40,42] only six studies employed randomization;[32,33,35,37,41,43] and only two of the studies were clearly and adequately blinded.[32,43] Among all of the published studies, only four meet or come close to meeting current standards. These studies are described in more detail below.

Additionally, many of the studies were not designed using the principles of good lactation management. In only a few studies were mothers provided instruction on proper breastfeeding technique.[30,32,37,40–42] Another difference among the studies is variability in the dosage of metoclopramide used. Although 10 mg three times daily was the most common dosage and the dosage shown to be optimal in a dose-ranging study among women with a faltering milk supply,[35] daily dosages ranged from 10 mg twice daily to 10 mg four times daily. The duration of treatment ranged from 1 week to 4 weeks, most commonly in the 10- to 15-day range.

In one early double-blind study, 20 women who had undergone delivery by emergency or elective Cesarean section were randomized to take oral metoclopramide ($n = 10$) 10 mg three times daily or placebo ($n = 10$) for 7 days beginning on the first day after Cesarean section.[37] All mothers expressed a desire to breast-

feed their infants for at least 3 months, and received daily visits by an investigator to discuss breastfeeding problems and were given advice and encouragement to breastfeed. The mothers in the two groups were closely matched except that three preterm infants in the metoclopramide group were separated from their mothers in the intensive care unit and were nursed there initially and fed expressed milk until discharge. At 10 days postpartum, there were no differences in the number of infants being breast fed in each group; at 6 weeks postpartum, nine women were breastfeeding in the metoclopramide group and eight in the placebo group; and 3 months postpartum four were breastfeeding in each group.

Although this was a small study, it was well designed and executed. It provided preliminary evidence of the benefit of patient counseling and encouragement on breastfeeding success.

Thirteen primiparous nursing mothers without breastfeeding difficulties and normal infants were given either oral metoclopramide 10 mg three times daily ($n = 7$) or placebo ($n = 6$) for 8 days beginning on the first day postpartum in a randomized, double-blind study.[43] No attempt was made to improve nursing technique, but mothers nursed on a 3-hour schedule beginning at 6:30 a.m. on the day following delivery. No mention was made of the type of feeding or the number of feedings that the infants received between birth and the initiation of breastfeeding or any differences in the two groups of infants in this regard. All women completed the trial. No differences were found in serum prolactin of treated and control women throughout 28 days of observation. Milk intake as measured by infant weight change before and after the second daily feeding on days 3 through 8 was greater by an average of 24.3 mL (51.1 mL vs 75.4 mL) in the infants of treated mothers. This difference was statistically significant overall; however, statistically significant differences in milk production did not occur until day 5 postpartum. Treated mothers had an earlier increase in milk amino acid content that the authors attributed to a more rapid transition to mature milk.

This paper has several flaws related to its analysis. The paper does not state the number of feedings per day, so the fraction of the infant's daily feedings that the one feeding represented is unknown. Even if this had been stated, the volume of milk can vary considerably from feeding to feeding.[5,6] We believe these problems probably invalidate the study's results.

Fifty mothers who had complete or partial lactation failure received extensive instruction on how to increase their milk supply.[41] Their infants were hospitalized for various illnesses and ranged from 29 to 100 days of age. Maternal lactation history was comparable in the two groups. Mothers were randomized either to receive or not receive metoclopramide 10 mg three times daily for 10 days. Although no specific metoclopramide placebo was given to control mothers, all mothers received multivitamins, iron, and folic acid daily, which the authors used to obscure to the mother whether she was receiving an active drug or not. All infants were put to the breast for at least 15 minutes, and those infants who were not sated were given additional nutrition afterward. No statistically significant differences were found between the groups in the time to initiation of milk secretion, to partial restoration of breastfeeding, or to complete breastfeeding or in the weight gain of the infants during the study period of 96 days. The authors concluded that successful relactation can be accomplished without galactagogues such as metoclopramide.

This study lacked a true placebo control which might have resulted in unblinding of the subjects, the investigators, or both. However, it employed excellent breastfeeding instruction and infant evaluation techniques that are well described in the paper. It also has the best overall design of any of the studies on mothers who had older infants and well-documented insufficient milk supplies at the start of the study.

In a well-controlled and analyzed, randomized, double-blinded study of the mothers of premature (23 to 34 weeks) infants, mothers received either metoclopramide 10 mg three times daily ($n = 31$) or placebo ($n = 29$) for 10 days beginning within 96 hours of delivery.[32] The groups were well matched and all mothers received standardized instructions from a lactation consultant and provided access to breastfeeding support. No selection was made for mothers who were having difficulties pro-

ducing milk. Milk was expressed using a Medela Classic electric breast pump, and milk volume was measured by mothers for 17 days after delivery with verification by investigators on two occasions during this time. No differences were found in the volumes of milk produced by treated and placebo mothers during or after cessation of metoclopramide therapy, no decrease in milk supply was seen after discontinuation of metoclopramide in nursing mothers, and no differences were seen between the groups in duration of lactation. Six subjects each in the drug and placebo groups dropped out for a relatively high dropout rate of 17.4%.

Although by far the best designed and executed study to date on any galactagogue, the study enrolled all mothers of preterm infants without any evaluation of their ability to produce milk. This population may, in general, need lactation support, but the possible inclusion of women in both the active drug and placebo groups who would have had little difficulty in milk production may have minimized differences between the groups. Intention-to-treat analysis was also used which is appropriate, but tends to attenuate differences between the two groups if there is a relatively high dropout rate as in this study.[44]

Domperidone

Domperidone is a gastrokinetic agent that is not U.S. Food and Drug Administration (FDA)-approved for sale in the United States; however, it is available from sources outside the United States and from compounding pharmacies in the country. It increases serum prolactin in lactating and nonlactating women.[45–47] In nonpregnant women, domperidone is less effective than the same dose of oral metoclopramide in raising serum prolactin; however, in multiparous women their effects are similar.[45,46] The use of domperidone as a galactagogue was first reported in 1983.[48] Fewer studies have been performed on domperidone than the other two drugs, and study populations have been quite small.

One paper, which was published twice in two different journals and languages, reported two separate small studies.[49,50] Both studies have serious flaws, but they are reviewed here because they are often cited as proof of domperidone's efficacy as a galactagogue. In the first study, 15 women with a history of defective lactogenesis were given either oral domperidone 10 mg ($n = 8$) or placebo ($n = 7$) 3 times daily from day 2 to 5 postpartum. The study was apparently not randomized, and blinding was not mentioned. No instruction or support in breastfeeding technique was provided, and the mothers fed their newborns 7 times daily. The groups had similar serum prolactin levels at the start of the study and basal serum prolactin levels were higher in the treated women from day 3 to 5 postpartum. Suckling-induced serum prolactin increases were higher in the treated women than in the placebo group from day 2 postpartum onward. Milk yield was calculated by weighing the infants before and after each nursing for 24 hours. Increases in milk yield were greater in the treated mothers from day 2 onward; however, the lower average milk yield in the placebo group was caused by three women with very low milk output. Average infant weight gain was correspondingly greater in the treated group. At 1 month postpartum, all treated mothers were nursing well, but five of seven untreated mothers had inadequate lactation. The study found no correlation between basal serum prolactin or the drug-induced increase in prolactin and milk production.[49,50]

In the second study reported in the same two papers, 17 primiparous women who had insufficient lactation (30% below normal) at 2 weeks postpartum were studied using the same methodology as above. Mothers were given either oral domperidone 10 mg ($n = 9$) or placebo ($n = 8$) 3 times daily for 10 days. Mothers in this study fed six times daily. The groups did not have statistically different serum prolactin levels at the start of the study. Serum prolactin levels were higher in the treated than untreated women from day 2 onward, and milk production was higher in the treated group from day 4 onward. At the end of the study no untreated woman had an increase in milk supply from day 1. One month after the beginning of the study, all treated women had adequate milk production. Again, no correlation was found between serum prolactin and milk production.

Because of their apparent lack of blinding and randomization and inadequate amount of breastfeeding by the subjects, these studies cannot be considered adequate to prove or disprove the efficacy of domperidone as a galactagogue.

Only one well-designed domperidone trial has been published.[51] Twenty women with preterm infants had failed to produce sufficient milk for their infant after extensive counseling by lactation consultants. All were pumping milk with a Medela Lactina double breast pump and were given either oral domperidone 10 mg ($n = 11$) or placebo ($n = 9$) 3 times daily for 7 days in a randomized, double-blind fashion. The mothers averaged 32 to 33 days postpartum. Serum prolactin levels were similar at baseline, 12.9 and 15.6 mg/L in the domperidone and placebo groups, respectively. By day 5 of therapy, the serum prolactin levels of the treated mothers had increased to 119 μg/L in the treated group compared to 18 μg/L in the placebo group. Serum prolactin decreased to baseline levels in both groups 3 days after discontinuation of the study medications. The paper did not state when in relation to nursing the blood samples for prolactin were collected. The baseline milk production was partially imputed in one domperidone patient and three placebo patients using day 1 results as baseline values. Baseline milk production was much greater in the domperidone group (113 mL daily) than in the placebo group (48 mL daily). The average daily increases in milk production on days 2 to 7 were 45% (to 184 mL) and 17% (to 66 mL) in the domperidone and placebo groups, respectively. However, four women in the domperidone group failed to complete the study, and only the study completers were matched and found to be similar at baseline (i.e., intention-to-treat analysis was not performed). No follow-up beyond the 7-day study period was done to evaluate the persistence of an effect of domperidone on lactation success or on adequacy of infant weight gain.

Although this study appears to offer evidence of a beneficial effect on the milk supply in the mothers of preterm infants who are pumping their milk, the great difference in baseline milk supply between the domperidone and placebo groups is of concern. It is possible that women with more severe underlying lactation problems were randomized by chance to the placebo group, skewing the final result in domperidone's favor. The 36% dropout rate in the active drug group is also problematic. Dropout rates of 20% or greater yield unreliable results.[44,52] This study cannot be said to offer unequivocal evidence for the utility of domperidone as a galactagogue.

Sulpiride

Sulpiride is a substituted benzamide antipsychotic drug that is chemically related to metoclopramide. It is an antagonist of dopamine at the D2, D3, and D4 receptors that increases serum prolactin levels similar to the other galactagogues. The first report of its use as a galactagogue was in 1978.[53] Sulpiride is not marketed in the United States, but is used outside the United States as a galactagogue.

Several studies have been published on the use of sulpiride in enhancing lactation.[54–60] As with the other galactagogues, most of the studies have design flaws. Although these studies were all placebo controlled, only three of the studies were clearly blinded and randomized. Only the studies meeting all of these criteria are reviewed.[57,58,60]

In one study, 28 women with self-reported insufficient lactation were randomized to sulpiride 50 mg ($n = 14$) or placebo ($n = 14$) three times daily for 4 weeks.[60] Women were within 4 months postpartum and the average ages of their infants were 62 and 56 days in the sulpiride and placebo groups, respectively. The two groups were fairly well matched at the initiation of the trial except that mothers in the placebo group had been supplementing for longer than women in the sulpiride group, 33 and 22 days, respectively. Mothers were given no instruction on breastfeeding technique and breastfed their infants 5.3 times daily on average. Infants were weighed before and after each feeding for 24 hours to determine daily milk production at baseline and six times during the 28-day study. Two women in the placebo group dropped out of the study and were not included in the final analysis. Serum prolactin was not significantly different between the two

groups at just under 100 μg/L at the start of the study. Serum prolactin 1 to 3 hours after the last daily dose rose in sulpiride-treated patients to about 400 μg/L and fell slightly in placebo-treated patients. Neither milk yields at the beginning of the study nor increases in yield showed any relationship to increases in serum prolactin. Infant weight gain was greater in the treated patients at the end of the study (1081 vs. 795 g); however, only four infants in the sulpiride group and none in the placebo group no longer required supplementary feeding at the end of the study.[60]

Although well designed, this study has several shortcomings. Serum prolactin measurements were timed in relation to tablet ingestion, not nursing, so it is not possible to state whether the values reported represent basal prolactin, stimulated prolactin or some value in between. Mothers in the placebo group had been supplementing longer than those in the sulpiride group, so may have had more intractable lactation problems; and the daily number of breastfeeds was low by today's standards. Also, most of the infants in both groups were supplemented, but the amounts of supplementation were not reported, making it impossible to tell if the additional weight gain in the sulpiride group was caused by increased milk production or by the supplementation.

A randomized, placebo-controlled trial studied 66 primiparous mothers with normal infants who expressed a desire to breastfeed, but only 41 mothers completed the study: 21 sulpiride and 20 placebo.[57] Mothers were blinded, but the paper does not state if the investigators were blinded. Mothers were apparently given no lactation instruction. The treatment group received sulpiride 100 mg three times daily for the first 4 days postpartum, then 50 mg three times daily for the next 86 days. Mothers were evaluated six times during the 90 days. The mothers who received sulpiride maintained elevated baseline serum prolactin levels of 117 to 119 μg/L throughout the 90-day study period. Mothers taking placebo had a normal drop in serum prolactin from 113 μg/L on day 1 to 20 μg/L on day 90; however, on days 4, 15, and 30, their 30-minute post-suckling prolactin levels reached about the same levels as the sulpiride-treated mothers who had only small increases in prolactin after nursing. At days 60 and 90, women taking placebo had much lower baseline and post-suckling prolactin levels than treated women. Infant weight gain was greater in the infants of treated women up to day 15, but there was no difference in weight gain between the groups thereafter. The authors noted the transient effects of the drug.[57]

This study suffered from a high 38% dropout rate, which makes intention-to-treat analysis unreliable. No explanation was given for the extremely long duration of treatment, but the drug appeared to produce no benefits beyond day 15. Nevertheless, the study reinforces the lack of correlation between serum prolactin levels and milk production and provides some evidence that use of galactagogue beyond 2 weeks provides no additional benefit, at least in women with no demonstrated lactation difficulties at the start of treatment.

A randomized, double-blind trial studied 60 women who were 25 to 40 days postpartum, 40 with insufficient lactation averaging 293 mL/day and 20 with no milk production at the start of the study. No mention was made of any lactation education given to the subjects before or during the study or the frequency of nursing during the study. Subjects were given *l*-sulpiride, *d*-sulpiride or *d,l*-sulpiride 50 mg twice daily or placebo for 15 days. Milk production increased in all drug groups. All women with insufficient lactation, including those receiving placebo, could avoid supplementation after 6 days of therapy. Women with no milk production at the start who received a drug were able to stop supplementation after 10 to 15 days; those in the placebo group were not able to breastfeed at the end of the study. The authors state that the increased milk production declined progressively after drug discontinuation, but did not provide any data.[58]

This study is one of the strongest arguing in favor of the efficacy of galactagogues in women with documented low production of milk. However, it is interesting that even placebo-treated patients with some initial milk production were able to stop supplementation at the same time as the treated women, even though their milk volume was less. The study indicates that women with no milk production might be

reasonable candidates for a galactagogue. It would be of interest to know if these effects persist if modern lactation techniques were employed before the study.

SAFETY

Milk and serum levels

The safety of using the dopamine antagonists as galactagogues has not been well studied. One method of judging safety is the relative dosage that the infant receives compared to the maternal dosage. Two studies have measured the amount of metoclopramide in breastmilk with a dosage of 10 mg three times daily. These studies found that an exclusively breast-fed infants would receive an average 1% to 2% of the weight-adjusted (i.e., mg/kg) maternal dosage.[32,34,61] The average absolute dosages that the infants would receive were 5.2 and 11 μg/kg/day in the two studies.[32,34,61] These values are considerably less than the dosage of 600 μg/kg/day reportedly used to treat gastroesophageal reflux in newborns.[62] However, one infant had serum levels of 20.9 and 18.6 μg/L on days 4 and 14 postpartum, respectively. These levels averaged 8% of the infant's mother's metoclopramide serum levels which were very high.[34] A study of neonates who received a single oral dose of 100 to 150 μg/kg found peak serum levels averaging 17.7 μg/L,[63] which is similar to the levels achieved in the breast-fed infant with metoclopramide detectable in serum.

Domperidone has been less well studied. The studies that have been performed did not carefully time milk sample collections. All three of these multidose studies used a domperidone dosage of 10 mg three times daily. Average relative infant dosages ranged from 0.04% to 0.08% of the maternal weight-adjusted dosage. Absolute infant dosages ranged from 0.17 to 0.39 μg/kg/day.[47,48,51] Since oral bioavailability of domperidone is about 15%, it is unlikely that pharmacologically meaningful amounts of domperidone reach the infant. No measurements of infant serum concentrations of domperidone from breastmilk have been reported.

Even less information is available on the excretion of sulpiride into breastmilk. Twenty women who were taking sulpiride 50 mg twice daily had a single milk sample from 2 hours after the morning dose analyzed. The average milk sulpiride concentration was 97 μg/L (range 26–197 μg/L).[56] This translates to an average maximum dosage of 0.9% (range 0.2–1.8%) of the weight-adjusted maternal dosage or 14.6 μg/kg/day (range 3.9–29.7 μg/kg/day) in the infant.

Side effect reports

In most studies of galactagogues, the methodology for detecting adverse reactions in the breast-fed infants has not been reported. Often it appeared to be casual observation by the mother or researcher. Many studies failed to mention infant safety at all.

A total of 143 infants have been reported in clinical studies on metoclopramide in which infant side effects were reported.[28,30,31,33–36,42] In one study of 37 women, an infant whose mother was taking oral metoclopramide 15 mg three times daily reportedly had intestinal discomfort. No infants whose mothers were taking a dosage of 5 or 10 mg three times daily or placebo had any adverse effects.[35] In another study, 23 premature infants had no adverse effects related to feeding tolerance or stool frequency during maternal metoclopramide therapy. The mothers were taking oral metoclopramide 10 mg three times daily for 7 days, with a tapering dosage for 2 more days, beginning at an average of 32 days postpartum.[30] Three studies measured serum prolactin in breastfed infants whose mothers were taking metoclopramide 10 mg three times daily. Of the 29 infants reported in these studies, three infants had elevations in serum prolactin.[31,33,34]

In addition to possible adverse effects on breastfed infants, a concern is maternal depression. Depression is listed as a possible adverse effect in the package insert; however, no studies have been performed to determine if depression is more prevalent or severe in mothers using metoclopramide than the background incidence of postpartum depression. One mother reported that she had increased intestinal gas during treatment.[36] Other side effects reported by nursing mothers receiving metoclopramide include tiredness, nausea, headache, vertigo, hair loss, and anxiety.[35,36]

Three studies on domperidone as a galactagogue were reported in two papers. A total of 28 women took domperidone 10 mg three times daily as a galactagogue. No side effects were reported in any of the breast-fed infants or their mothers.[49–51] Domperidone's popularity stems in part from its reputation of having lower penetration of the blood–brain barrier, and consequently, fewer central nervous system side effects than the other agents.[45] Although we could find no studies on the penetration of domperidone across the blood–brain barrier in humans, animal data appear to support the concept of poor central nervous system (CNS) penetration. This lack of penetration appears to be a result of extensive metabolism by CYP3A4 and pumping of domperidone out of the CNS by *p*-glycoprotein. These processes can be inhibited by concurrent medications, and their inhibition would result in greater CNS penetration.[64,65]

The FDA has warned against the use of domperidone as a galactagogue because no FDA-approved products are marketed and because cardiac arrhythmia, cardiac arrest, and death reported after intravenous administration of domperidone.[66,67] Since maternal serum levels of domperidone are much higher after intravenous than oral use, the relevance of these deaths to the use of oral domperidone as a galactagogue has been questioned.[68] However, domperidone can prolong the QT interval, particularly in the presence of potent CYP3A4 inhibitors such as ketoconazole (now listed as a contraindication to domperidone therapy by the manufacturer), erythromycin, and grapefruit juice, which can markedly increase systemic domperidone exposure.[65] A recent case–control study found that patients taking domperidone had a 3.8-fold (95% confidence interval [CI] 1.5 to 9.7) greater risk of sudden cardiac death than matched controls.[69] The cardiac risk to nursing mothers cannot be dismissed.

In two studies in which side effects were reported, a total of 38 women were given sulpiride 50 mg three times daily for 2 to 4 weeks. No side effects were reported in their breastfed infants.[54,60] However, use of sulpiride in other conditions has resulted in sedation, depression, sleep disturbances, restlessness, impaired concentration, extrapyramidal reactions, weight gain, xerostomia, and neuroleptic malignant syndrome.[70,71]

SUMMARY

Most studies on galactagogues do not meet modern of evidence-based medicine standards such as randomization, placebo control, and blinding. Many of the studies were performed before the advent of modern lactation management, and either infants were kept away from mothers so demand feeding could not take place or feeding was on a fixed schedule with an inadequate number of daily feedings. Few studies provided breastfeeding encouragement and instruction to mothers. Of the four well-designed studies that did provide maternal lactation education, three found that galactagogues made no difference in lactation success.[32,37,41] The fourth,[51] although very well designed, enrolled such a small number of patients that it had dissimilar study groups at baseline. It also suffered an untenably high dropout rate. These two shortcomings make the results of the study uninterpretable.

Another inconsistency among studies is the types of patients studied. Even some well-performed studies have studied "all comers," for example, all mothers delivering by Cesarean section,[37] all primiparous mothers with normal, full-term infants,[57] or all mothers of preterm infants[32] without first evaluating the need for a galactagogue. These selection criteria tend to dilute any possible differences between drug and placebo groups because some patients in both groups may not have had any lactation difficulties. In a study that enrolled only mothers with documented low milk production afer a few weeks, the galactagogue was effective in increasing milk volume, but it was only more effective than placebo in avoiding supplementation in those with no initial milk production.[58]

Adverse effects of these drugs when used as galactagogues have not been rigorously studied. Gastrointestinal upset[35,36] and elevated serum prolactin in breastfed infants have been reported with metoclopramide.[34] These effects may be related to the occasionally high breastmilk and infant serum levels. An increased risk

of maternal depression is a concern with metoclopramide and sulpiride that has not been adequately evaluated. Domperidone has very low levels in milk, poor oral bioavailability, and probably has lower penetration across the blood–brain barrier. Safety for the mother has not been established, but reports of QT prolongation and increased risk of sudden death after oral use are troubling.

CONCLUSIONS

Of a small number of studies from which one can glean reliable information, it appears that a few generalizations might be made:

1. Dopamine-antagonist galactagogues raise baseline serum prolactin in nursing mothers.
2. No direct correlation has been demonstrated between baseline serum prolactin and long-term breastfeeding success in normal women or in those given a dopamine antagonist galactagogue.
3. Presumptive use of galactagogues in unselected patients in populations that sometimes have difficulty nursing such as mothers who have had a Cesarean section, or who have preterm infants appears to be of no benefit.
4. If mothers are provided education and practice techniques that support lactation physiology, galactagogues appear to have little or no added benefit.
5. The safety of dopamine antagonists has not been adequately studied when used as galactagogues, but all have potential safety concerns for mothers, infants, or both.

Healthcare providers and women for centuries have been searching for a "magic bullet" to solve breastfeeding problems. Fortunately, breastfeeding problems can be prevented and resolved in the vast majority of patients by practices known to support lactation physiology. Galactagogues should not be used as a substitute for good patient management. Women who might need a galactagogue temporarily to increase milk supply are those who cannot produce sufficient milk after these measures have failed. Large, well-designed studies in these women may be justified.

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