Introduction

Lactation can be divided into the consecutive stages of mammogenesis (development of mammary tissue), lactogenesis (production of colostrum and first milk) and galactopoiesis (maintenance of milk production under suckling and/or milking stimulus). Mammary growth and development, milk production, milk ejection and mammary involution are under the control of different hormone systems: progesterone and growth hormone act synergistically to cause mammary gland development, prolactin acts towards the end of pregnancy to start lactation and oxytocin causes milk letdown. Once suckling stimuli cease, insulin-like growth factor-I (IGF-I) is secreted in large amounts causing mammary gland involution, following which the mammary gland remains in a quiescent state for a few months. The control of different mammary functions relies on understanding how these different hormone systems and their stimulating/inhibiting factors exert their action. This paper will review the endocrine control of mammary functions in bitches and queens, as well as pharmacological treatments which can be used by small animal clinicians to treat bitches or queens with hyper- or hypo-function of the mammary gland. As the literature on physiology of the mammary gland of small animals and its normal or abnormal functions is very scant (canine) or almost non existant (feline) - with the only exceptions of mammary tumors or mastitis - the reader should be aware that a) majority of the information presented in this paper is drawn from work done (mostly) in humans or other animal species, and b) the majority of clinically relevant conclusions are extrapolated from data coming from humans or other animal species. However, it is noteworthy that mammary gland function is fairly similar across species, as it can be inferred by similarities in the action of endocrine drugs on lactation in different animal species as well as humans. Conditions such as mastitis or mammary neoplasia are beyond the scope of this paper and will not be discussed here.

Keywords: Mammary gland function, antiemetic, antipsychotic, dopamine agonists, serotonin antagonists

Mammary physiology

Mammary growth

Mammary proliferation starts at birth and is minimal (proportional to body growth) until puberty, when a rapid extension and branching of the duct system starts. Thereafter, the degree of mammary growth depends on the stage of the reproductive cycle, being maximal during gestation, early postpartum and in general during steroid-regulated phases, and minimal during anestrus. Growth is generally characterized by duct extension and branching followed by proliferation of lobules and alveoli, with the proportion of parenchyma to stroma increasing exponentially such that in early postpartum period, the mammary gland is composed of a network of lobes and lobules separated by fine septa of connective tissue. Unlike what used to be thought, mammary growth is not limited to gestation but can continue also at the end of pregnancy and into the early stages of lactogenesis.1

The role of sex steroids in regulating mammogenesis is very similar in different species, and is characterized by the pivotal actions of 17-b-estradiol (E2) and progesterone (P4) in causing proliferation of the ductal and lobulo-alveolar components of the mammary gland, respectively, and in maintaining the mammary epithelium in a steady state (the so-called “survival action”).2,3 Ample clinical as well as experimental evidence clearly indicates the importance of estrogen signalling for normal mammary development: mammary growth (particularly ductal growth) does not occur in castrated individuals or in mice deprived (knockOut = NO) of the estrogen receptor, whereas it resumes following estrogen administration. In these estrogen receptor NO mice, complete mammary ductal growth requires administration of E2, growth hormone (GH) and adrenal corticosteroids; if P4 and prolactin (PRL) are added to this combination, normal lobulo-alveolar growth resumes.4,5 In the postpuberal bitch, GH plays a role in the development of mammary tissue acting in concert with GH induced IGF-I and some of the IGF-binding proteins;6 lobulo-alveolar growth and development
mainly occur during the second part of the canine luteal phase, with maximal development coinciding with the highest plasma PRL concentrations, a well-established feature of the second half of the canine diestrus.\textsuperscript{7} Canine GH secretion, arising from foci of hyperplastic ductular epithelium of the mammary gland, is influenced by P4\textsuperscript{8} and occurs during phases of high serum P4 concentrations (such as during the first half of the luteal phase in the bitch).\textsuperscript{7,9}

Milk production

Once lobulo-alveolar growth has occurred, alveolar epithelial cells acquire the capacity to secrete milk through organellar and biochemical differentiation. This stage is normally reached when parturition approaches, as typically the first milk secretions can be observed prior to delivery. Soon after parturition and for the first few days a thick, often yellowish milk is produced (colostrum). This phase is normally referred to as lactogenesis, while the maintenance of sustained milk production for weeks or months thanks to suckling (or milking) is called galactopoiesis. During lactogenesis and galactopoiesis, PRL and GH play a fundamental role in controlling milk production in most species studied, including dogs and cats.

While the influence of GH dominates over that of PRL in ruminants, PRL is very important for lactogenesis and galactopoiesis in rodents, humans as well as dogs\textsuperscript{10} and presumably cats. In the dog, pituitary secretion of PRL is modulated by both stimulatory and inhibitory signals: dopamine is the main inhibitory factor, while several substances, including serotonin and thyrotropin-releasing hormone, have PRL-releasing properties.\textsuperscript{11} Progesterone has an important modulatory effect on canine PRL secretion: when P4 concentrations are high, PRL is low or non-detectable; when P4 decreases after having been at high concentrations for a prolonged period (such as at the end of diestrus), PRL secretion is stimulated and a peak occurs. This is confirmed by the observation of high PRL concentrations in pseudopregnant as well as periparturient bitches (as both conditions require a drop on serum progesterone). Also, in pregnant bitches, PRL rises around day 35 after the LH peak;\textsuperscript{10} such a rise occurs at a time when serum P4 starts to decrease, confirming the importance of P4 in modulating PRL release from the pituitary. No progressive increase in PRL secretion occurs in non-pregnant bitches at the same time interval after the LH peak.\textsuperscript{10} However, PRL concentrations rise in non-pregnant dogs at the end of diestrus causing pseudopregnancy. The importance of P4 in regulating PRL secretion is further confirmed by:

a) the capacity of progestogens to eliminate clinical signs of pseudopregnancy by decreasing PRL levels; PRL will rebound once progestogen treatment is withdrawn, which would be expected as it escapes P4 regulation. For this reason progestogens should not be used for the treatment of pseudopregnancy.

b) the fact that administration of a progesterone-receptor antagonist to pregnant bitches results in highly elevated plasma prolactin levels.\textsuperscript{12}

At the mammary level, PRL and GH induce functional differentiation through milk protein and fatty acid synthesis, with the transcription of several milk protein genes on the mammary epithelial cells being significantly increased during mid-lactation as compared to the onset of lactation.\textsuperscript{13} The importance of PRL for stimulating lactogenesis and galactopoiesis is confirmed by the effectiveness of PRL-releasing drugs (see below). Unlike for PRL receptors, there is little evidence of the presence of GH receptors at the mammary level. Growth hormone is found in canine and feline mammary gland tissue and secretions (particularly pre-partum and in colostrum) at high concentrations, up to 100-1000 times those in plasma;\textsuperscript{6} however, canine fetuses do not show any evidence of increased GH levels, and there is no correlation between milk GH and neonatal GH due to poor absorption of GH at the gastrointestinal level.\textsuperscript{14,15} Therefore, the action of mammary GH on mammary growth and secretion as well as the role of milk GH remain unclear in the bitch as well as in other species.

Oxytocin plays an important role in milk ejection by causing powerful contractions of the myoepithelium surrounding alveolar ducts. Its release from the hypothalamus (supraoptic and paraventricular nuclei) is modulated by sensory stimuli arising from suckling at the teats. It is currently believed that oxytocin does not interfere with the process of milk production,\textsuperscript{16} but rather exerts its action on milk letdown. Its indications in human and veterinary include only obstetrical problems (dystocia) and the treatment of postpartum hemorrhage. The claim that it may help to
increase milk yield are so far unsubstantiated, as no connection has ever been established between oxytocin and PRL secretion. In dogs, peak lactation is assumed to occur around the third to fourth week postpartum as puppies do not start eating semisolid food until their deciduous teeth erupt at 21-35 days of life. Normal puppy growth is generally supported by the dam’s milk up to four weeks postpartum, after which reduced growth will occur if supplemental food is not provided. At peak lactation, daily milk production is approximately 1.7 kg milk/day in German sheperds and 1.0 kg/day in Beagles.¹⁷

Mammary involution

Once the suckling/milking stimulus is withdrawn, the mammary gland starts a gradual involution process through which it reverts back to a state of development only slightly greater than what existed at puberty. Such regression (which is normally faster if suckling/milking ceases in early lactation) is due to withdrawal of galactopoietic hormones with consequent decrease in the expression of genes responsible for milk synthesis, and therefore a decrease in milk secretion. The immediate drop in the concentrations of PRL and GH once milking or suckling stimuli cease is a mechanism demonstrated in rodents and confirmed in ruminants.¹⁸,¹⁹ The involution effect is due to the lack of anti-apoptotic action which PRL exerts on mammary epithelial cells, and is directly proportional to the magnitude of decrease in PRL. In lactating Beagle bitches, PRL reaches its peak concentration shortly after delivery, after which it plateaus for a few weeks and then starts a gradual decrease reaching basal values around two months post-partum.¹⁰ Canine mammary involution starts around the end of the second month of lactation.²⁰ In rodents and in ruminants, PRL is regarded as one of the principal endocrine signals in controlling and preventing mammary cell death. In fact, its administration following litter removal in mice delays mammary apoptosis, and its decrease following use of anti-PRL agents rapidly induces apoptosis and cell loss associated with a consistent reduction in milk yield. These observations, combined with the well known involutionary effect of antiprolactinic agents on the canine and feline mammary glands,²¹,²² probably indicate that a similar mechanism occurs in small animals as well. In addition to the regulatory role of sex steroid hormones on mammary function, a wealth of novel information has been obtained on the role of E2 and P4 receptor expression and their cross-talk with the receptors for some growth factors (such as epidermal growth factor, tumor necrosis factor alpha, etc.) during lactation as well as mammary involution in experimental animals. However, these mechanisms have not been studied in carnivores and their relevance in clinical practice remains to be determined.

Pharmacological control of mammary function

Control of mammary function normally refers to stimulation or inhibition of lactogenesis and galactopoiesis, as both processes can be controlled to a great extent in humans and animals. In domestic animals, the endocrine mechanisms controlling cessation of milk production and mammary involution are more clearly defined than those controlling mammary growth and lactation. Because of a) the pivotal role played by PRL in promoting mammary growth and milk secretion, and b) the availability of PRL-lowering drugs for use in small animals, it is relatively easy to inhibit mammary function thus stopping lactation. Conversely, it is not as easy to stimulate mammary growth and lactation, particularly in bitches and queens.

Increasing milk production

Conditions in which it is necessary to increase milk production in bitches and queens include insufficient or absent milk production (generically referred to as hypogalactia or agalactia, respectively) due to inadequate mammary development during gestation. Milk production may however be lower than normal despite normal mammary development, in which case the cause of abnormal lactation is presumably due to failure of endocrine mechanisms responsible for lactogenesis and galactogenesis to activate, thereby resulting in decreased or absent PRL secretion. As with most other hormonal secretions, stress will interfere with PRL release from the pituitary; therefore, causes such as mastitis, metritis, endotoxemia, systemic illness or psychological problems may be responsible for lack of onset of lactogenesis and/or galactogenesis. Agalactia is a rather obscure condition in bitches and queen, while it has been extensively studied in women. Milk production in breastfeeding mothers can be increased using a variety of drugs called galactogogues. These include
antiemetics such as metoclopramide and domperidone; antipsychotics such as chlorpromazine and sulpiride; hormones such as oxytocin, growth hormone and medroxyprogesterone acetate. The human literature will be briefly reviewed here as the treatment of agalactia in small animals relies entirely on drugs of the human pharmacopeia.

**Antiemetics.** Metoclopramide is a central nervous system (CNS) dopamine D2 receptor antagonist used as a human antiemetic drug. Recommended dosages for galactogenic effect in women are 10-15 mg/day TID, per os for 3-4 weeks. Its antagonizing action on the main PRL inhibitor dopamine causes a powerful, albeit indirect stimulus to PRL release with reported high efficacy rates especially when metoclopramide is associated with oxytocin nasal spray. In lactating women, metoclopramide is transferred to breast milk where it quickly becomes more concentrated than in plasma (milk-to-plasma ratio of 1.8:1), although this is not regarded as critical for babies since the milk level is below pharmacological doses. Metoclopramide acts also as an antagonist of serotonergic receptors (although this does not prevent PRL-releasing action), and has some cholinergic effects on smooth muscle. Maternal side effects include tiredness, headache, anxiety, nervousness and intestinal disorders. At higher doses (2-5 mg/kg) the drug may penetrate the blood-brain barrier and extrapyramidal signs (anxiety, agitation, movement disorders, dystonic reactions, ataxia) are reported.

Metoclopramide is also normally used in dogs as an antiemetic drug at oral dosages between 0.2-0.4 and 1-2 mg/kg divided in 2-3 administrations. It has been used also to stimulate canine PRL secretion, although scientific data with pre- and post-treatment PRL concentrations are available only for male dogs, in which a significant increase in serum PRL concentration is reported following treatment with 0.2 mg/kg 3 times daily. Use of metoclopramide in bitches with agalactia is anecdotal, with protocols varying from low (0.2-0.5 mg/kg SC or PO, BID or TID) to high dose regimens (1-5 mg/kg beginning PO or SC, every 6-8 hrs). Efficacy seems to be adequate with (subjective) improvement of milk production in ≥50% of cases, although no data on PRL concentrations pre- and post- treatment are available. Extrapyramidal signs may occur in canines, and are a concern in nursing bitches, therefore higher dosages should be avoided. Improvement in milk production is generally noticeable within 24-48 hours. To minimize side effects, it is advisable to start at a lower dose (0.5 – 2 mg/kg/day divided TID) for the first 24-48 hours and then if there is no improvement gradually increase the dose every other day until an effect or abnormal clinical signs are noted, at which point the dose is dropped to the prior day’s dose or discontinued. Extrapyramidal signs are much more common at doses above 2 mg/kg/day. Bitches should be monitored carefully when being treated with metoclopramide to ensure injury to the pups does not occur. Treatment should be continued for at least two to three days beyond when milk production appears to be resulting in adequate daily weight gain for the pups without supplementation.

Domperidone is a peripheral dopamine receptor antagonist developed as an antiemetic agent and used for the treatment of nausea and vomiting. In women, domperidone significantly increases PRL secretion thereby enhancing breast milk production, and is therefore used (off-label) as a galactogogue in most Western countries. In 2004, a few cases of cardiac arrhythmia and sudden death were observed in US patients suffering from cancer and with low potassium who were receiving high IV doses of domperidone concurrently with chemotherapy. This prompted an FDA warning that breastfeeding women should not use domperidone, after which the drug was subsequently withdrawn from the US human market. Subsequent research has shown that domperidone is safe when used by lactating mothers. The maximum approved treatment protocol of domperidone in lactating women is 20 mg given four times daily, although most authors advise using doses of 10 mg orally TID for one to two weeks. However, the minimum effective dose and the minimum duration of therapy have not been identified yet. Domperidone causes a significant increase in serum PRL concentrations and milk production in treated vs control mothers, which has been estimated at 75% in a recent meta-analysis. Unlike metoclopramide, domperidone is less permeable to the blood-brain barrier and is transferred in moderate quantities to maternal milk (milk-to-plasma ratio of 0.2-1.1), due to its high molecular weight and its 90% binding to plasma proteins. No side effects are reported in infants of mothers taking domperidone, while side effects in mothers include oral mucosal dryness, skin eruption, itch, headache and gastrointestinal disorders; extrapyramidal effects have been observed (dystonia) but are rare. No difference in milk quality of mothers treated with domperidone is reported, except for significant increases in carbohydrate and calcium.
Early experimental use of domperidone has been reported in the dog, with data on pharmacokinetics and excretion and metabolism in Beagle dogs. However, there is a lack of scientific as well as anecdotal information on clinical use of domperidone in small animals with low milk production. This is surprising given the positive results and the lack of side effects of this drug making it probably the best treatment for increasing milk production in lactating mothers. Domperidone is known among small animal clinicians by “word of mouth” to be effective in improving milk yield at doses of 1.5-2.0 mg/kg in queens, and 2.2 mg/kg in bitches, per os for one to three weeks. Treatment should be continued for at least two to three days beyond when milk production appears to be resulting in adequate daily weight gain for the pups without supplementation. In our experience, results of domperidone in increasing milk production in agalactic bitches and queens appear to be positive, better than those obtained with metoclopramide and devoid of extrapyramidal effects. Diarrhea is the most common side effect in the bitch, although there are anecdotal reports of behavior changes in some bitches being medicated.

**Antipsychotics.** Chlorpromazine is an antagonist of D2 dopaminergic hypothalamic receptors, commonly used for the treatment of human psychosis including schizophrenia and depression. It is considered the prototype of the phenothiazine class of drugs. Its action on dopaminergic receptors causes PRL release, which is the reason for its off-label use in breastfeeding mothers. It is transferred to milk in low quantities (milk:plasma ratio of 0.5), and its recommended dosage for galactogogic effect is 25 mg orally TID for one week. Chlorpromazine has a wide action on different CNS receptors producing also anticholinergic, antihistaminic, as well as weak antiadrenergic effects. The main side effects of chlorpromazine in psychotic patients (who are treated with higher doses than lactating mothers) are mostly due to its anticholinergic properties and include sedation, slurred speech, dry mouth, constipation, urinary retention, possible lowering of the seizure threshold, increased appetite and impaired glucose tolerance leading to increase in weight. Not much is known about side effects of chlorpromazine in breastfeeding mothers and their infants, although lethargy, sleepiness and reduced activity have been reported in a few babies. For these reasons, the American Academy of Pediatrics (AAP) in 2001 stated that chlorpromazine is included in the list of drugs whose effects on nursing infants may be of concern, and some authors advice monitoring of infants whose mothers are under chlorpromazine treatment.

In small animals, chlorpromazine is used as a second choice antiemetic drug when metoclopramide does not work and blood pressure is normal. Suggested antiemetic dosage is 0.2-0.5 mg/kg every 6-8 hrs. Only anecdotal information on the use of chlorpromazine in cases of agalactia is available for small animals. Some authors advise the use of acepromazine at 0.125-0.5 or 0.5-2.0 mg/kg, SC 2-3 times/daily. No data on clinical efficacy in bitches or queens as well as milk:plasma ratio of transfer are available for this drug.

**Sulpiride** is a substituted benzamide used as an antipsychotic drug for the treatment of human psychosis including schizophrenia and depression. It is a strong antagonist of serotoninergic receptors as well as of muscarinic, alpha-adrenergic and histaminic receptors. Its administration (off-label) to breast-feeding women in galactogenic doses of 50 mg orally 2-3 times/day for one to four weeks produces a strong PRL-releasing effect with PRL reaching serum concentrations which may be up 90% higher than in the control group and infants of treated mother gaining significantly more weight than control ones. Significant increases in milk production are reported only for primiparous mothers, not multiparous. Milk of treated mothers shows presence of the drug, although the milk:plasma ratio of transfer is lower than with metoclopramide or chlorpromazine. Although side effects are extremely rare in mothers and have never been reported in infants of treated mothers, the AAP advises against use of sulpiride in breastfeeding women as it does with all neurotropic drugs. No information on the use of sulpiride in dogs or cats is available.

**Hormones.** Oxytocin causes contraction of the myoepithelial cells that surround the alveoli as well as contraction of milk ducts, causing milk ejection. Although available for several decades as a human drug for use during labor or for postpartum hemorrhage, little information is available on its use to increase milk production in women. Earlier studies reported a significant effect of one nasal spray/nostril (3 IU total) of oxytocin prior to manual expression. However, no significant effect on milk volume was observed in a recent double blind randomized controlled trial. A combination of oxytocin nasal spray and metoclopramide has given positive results on milk yield. There is no information on transfer of oxytocin to maternal milk in women, and no side effect has ever been
reported in treated mothers (except perhaps abdominal pain in women recovering from a cesarean section) or in infants. Despite limited scientific information, and despite its well known mechanism of action related to milk let-down, most human gynecologists consider oxytocin capable of increasing milk production and recommend its use when needed.

Oxytocin is widely used in small animals, mostly as a treatment for non-obstructive dystocia due to uterine inertia at doses ranging from 0.5 to 5.0 IU based on body weight. However, most if not all available information on its use during small animal dystocia is anecdotal. No dose-response studies have ever been performed in bitches or queens. Its use in case of agalactia is anecdotally reported as effective following repeated dosing with the nasal spray or with IV or IM administrations of 2-5 IU IM prior to each suckling.

Based on its mechanism of action, oxytocin will help to empty the mammary gland of previously produced milk, but it is unlikely to help increasing milk production by the mammary epithelium, unless poor suckling stimulus of puppies is causing failure of milk letdown due to back up pressure on the mammary epithelium. However, anecdotal evidence should not be dismissed as irrelevant as it may sometimes be a prelude to scientific findings; for instance, the anecdotal efficacy of oxytocin in improving milk yield in bitches might be due a potential (unknown) stimulatory effect of oxytocin on PRL secretion. Perhaps oxytocin’s greatest impact would be to assist nervous and primiparous bitches with milk letdown in the first hours or days postpartum. The combination of oxytocin in microdoses (0.5 – 1 IU/dog every 60 – 90 minutes, given 15-30 minutes prior to nursing) with dog appeasing pheromone spray (DAP Spray®, Ceva Animal Health, Rutherford, NJ) +/- a low dose of a sedative like acepromazine, can be highly beneficial in causing milk letdown until the bitch settles in with her litter. If a sedative is used, care should be taken to not make the bitch so tired that she cannot care for her litter properly or that she may become clumsy and lay on a puppy and smother it.

Decreasing milk production

Milk production can be easily inhibited in small animal thanks to the availability of antiprolactin compounds as veterinary (and human) drugs. Conditions for which milk production should be inhibited include pseudopregnancy in bitches, as well as mastitis in lactating bitches and queens. Also, inhibiting milk production should be taken into consideration at weaning, especially if galactostasis (mammary congestion) occurs, in case of eclampsia or for animals being prepared for mammary surgery. Antiprolactinic agents include dopamine agonists and serotonin antagonists.

Dopamine agonists. Both bromocriptine and cabergoline have a strong dopaminergic activity, and thus can reduce prolactin secretion by increasing the action of its natural inhibiting factor, dopamine. Bromocriptine is a non-specific D2-receptor agonist which has been available as a human drug in many countries of the world and used in veterinary medicine since 1980. Several therapeutic protocols have been proposed, with doses ranging from 10 to 100 μg/kg BID for 10–14 days. The human formulation (Parlodel™, Sandoz, Princeton, NJ) comes in 2.5 mg tablets, which makes fractioning necessary to achieve the correct dose for bitches, although treating small size dogs can be done by dissolving a single tablet in 10 ml distilled or sterile water in an amber vial, providing an equivalent of 250 mg/ml solution; the solution should be refrigerated and used within one week to maintain its effectiveness. The dose-dependent inhibiting effect of bromocriptine on PRL secretion is strong but relatively short-lived (half-life: ± 4-6 hours). Clinical efficacy in inhibiting mammary function in pseudopregnant bitches is achieved by administering bromocriptine BID at doses of 10-30 μg/kg, although doses as low as 7.5 μg/kg are reportedly effective. Its lack of specificity leads to side effects such as vomiting and anorexia (the most common ones, especially at doses > 30 μg/kg) due to stimulation of the chemoreceptor trigger zone, and less commonly (or with higher dosages) also affects the cardiorespiratory system such as hypotension due to vasodilatation (adrenergic type effect), and/or depression and behavioral changes. In our experience, gastrointestinal side effects can be lessened by giving the medication with food, while attempts to improve side effects by gradually increasing an initially low dose, or by pre-treated with an anti-emetic drug have proved only partially effective. Although its effectiveness has never been questioned, bromocriptine is not approved in most countries as an anti-PRL in small animals and its extra-label use has not caught on, in spite of its world-wide availability as a human drug.

Cabergoline is a synthetic ergot derivative with a long-acting, selective D2-dopamine antagonist effect, and low affinity for dopamine D1-receptors, α1-adrenergic-receptors and α2-
adrenergic-receptors. Following a single oral dose, absorption of cabergoline from the gastrointestinal tract is highly variable, typically occurring within 0.5 to 4 hours. Ingestion with food does not alter its absorption rate\textsuperscript{21,22,56} and longer than 48 hours due to its particularly long (minimum 48 hours) half-life at the hypophyseal level. This has clinical relevance, as unlike other antiprolactics requiring twice daily administrations, cabergoline can be given once daily. The most common side effect is vomiting, which appears to have a lower incidence with respect to other antiprolactic agents due to cabergoline’s specific D2-type action as well as to the fact that the drug rarely crosses the blood–brain barrier and consequently has much less central side-effects.\textsuperscript{21,22,56} The veterinary formulation comes as oral drops (Galastop™, CEVA) and its suggested dosage in bitches is 5 μg/kg (0.1 ml/10 kg) per day for five days, and in queens of 0.5-1.0 ml/cat. An injectable formulation has recently become available in Italy.\textsuperscript{57} When administered at the dose of 1.5 μg/kg injectable cabergoline is effective in reducing the circulating PRL concentration in lactating bitches, with mean PRL values showing an average reduction of 50% with respect to the placebo period three days after the administration, and PRL concentration remaining significantly low for 60 hours post-injection.

**Serotonin antagonists.** Serotonin is considered the main stimulating factor for PRL release. Therefore, a serotonin antagonist will depress PRL release by depriving pituitary lactotroph cells of a necessary stimulus. Metergoline is a synthetic ergot derivative which functions as a serotonin antagonist, and as such it deprives PRL secreting pituitary cells of a necessary trophic stimulus thereby inhibiting PRL secretion via an indirect mechanism. However, at high doses metergoline also displays dopaminergic effects\textsuperscript{50,58} Reported side effects include behavioral changes such as anxiety, aggressiveness, hyperexcitation and whining, which are due to its central antiserotonergic effect.\textsuperscript{48,59,60} Because of these central effects, metergoline should not be used in aggressive, anxious or nervous bitches or bitches with behavioral problems, as these may be exacerbated. Vomiting may occur, but is less common than with bromocriptine. Because of its short serum half-life metergoline’s antiprolactinic effect is lower than that of cabergoline and bromocriptine,\textsuperscript{61} although the veterinary formulation appears to be satisfactory for use in small animal practice when using the suggested lactation inhibiting dose of 100 μg/kg orally BID, to be continued for eight to 10 days. The veterinary formulation (Contralac™, Virbac Animal Health, Ft. Worth, TX) comes in 0.5 mg and 2.0 mg pills.

**Clinical considerations**

Because of the key role played by PRL in determining mammary growth and milk secretion, antiprolactinic agents constitute a very effective way to decrease milk production, such as in case of pseudopregnancy.\textsuperscript{22,56,58} Pseudopregnancy is a condition typical of canids which evolves as an adaptation from wild to domesticated life. As such, it should be considered as a physiological phenomenon which may or may not require treatment depending on how it develops. Development of mammary glands occurs normally during diestrus, and unless it is accompanied by milk secretion and nesting behavior it should not be a cause of concern or a reason for treatment. However, owners should be instructed that when milk secretion appears the bitch should be watched closely as this is often a threshold for initiating treatment, especially if accompanied by behavioral signs. Mild cases should be given a few days of close observation before treatment is instituted, as spontaneous remission is not uncommon especially if the bitch does not lick or suckle on herself. Stimuli such as licking, milking and the use of cold and hot packing should be avoided as they will cause oxytocin release (and might be associated with PRL release as well). Whenever licking or maternal behavior are displayed, pharmacological treatment to inhibit PRL secretion and mammary function may be instituted. Antiprolactinics are the drug of choice to stop milk production and eliminate behavioral signs in pseudopregnant bitches. In pseudopregnant bitches behavioral and mammary signs will disappear following treatment with a progestogen; however, a PRL peak frequently occurs when progestogen concentration declines following treatment withdrawal, which will cause the condition to recur. The PRL peak at the end of treatment is to be expected as this is what is observed at the end of a normal luteal phase,\textsuperscript{62} or when ovariectomy is performed during a luteal phase.\textsuperscript{63} Therefore, progestogens should never be used for treating canine pseudopregnancy.

The length of treatment of most antiprolactin protocols is five days. However, this duration of treatment is sometimes not sufficient to treat the condition successfully, and relapses are occasionally observed. When trying to inhibit mammary secretion, it is always advisable to treat for
at least 10 days, as this almost eliminate the risk of recurrence. Occasional failures can be dealt with by repeating the treatment course and also by using joint protocols of cabergoline+metergoline or cabergoline+bromocriptine. If an antiemetic becomes necessary (which is rarely the case with cabergoline and metergoline) its choice should be made with caution as many antiemetic drugs may cause PRL release in the dog and so are contraindicated since they are counterproductive. As to treatment choice, in a comparative study over time, changes in plasma prolactin concentrations after one oral administration of bromocriptine (25 µg/kg), metergoline (200 µg/kg) and cabergoline (5 µg/kg) were followed over a period of three days with frequent samplings; an effect of the three drugs was observed after 1.5, 4 and 4 hours, respectively. Maximum effects and interval to return to basal values were: bromocriptine four hours and lasting for ± two hours; metergoline four hours and lasting for two hours; cabergoline six to eight hours and lasting for up to 48 hours.64 Cabergoline seems to offer some advantages over other PRL-inhibiting substances. However, vomiting does occur occasionally, and sometimes a bitch will vomit with cabergoline and not with metergoline. Both drugs are considered effective, the only precaution being to avoid metergoline in bitches with behavioral problems.

Timing of antiprolactinic treatment has never been debated so far. Prolactin secretion has been reported to be pulsatile perhaps due to stimuli provided by suckling pups.65 A diurnal variation in serum PRL concentration was observed in three of ten anestrous bitches,66 with high values between 2:00 pm and midnight and low values from 1:00 am until noon. In a group of adult, lactating Beagle bitches we observed a clear circadian rhythm of PRL secretion, with the highest values found in the morning, and the lowest values found in the evening.57 These results need further investigation, as there might be differences in the mode or pulsatility of PRL secretion depending on the stage of the reproductive cycle or the condition of the bitch. Pulsatility of PRL secretion might be relevant for timing of antiprolactinic treatment: in fact, if a peak PRL secretion occurred in the morning it might be ideal to plan a once daily treatment starting in the morning rather than in the afternoon or evening.

Conclusions

Controlling mammary function is a topic which has been neglected in the veterinary literature, however it is becoming more common as a presenting complaint in small animal practice. Stimulating mammary growth and milk secretion remains a challenge, although there is a wealth of human drugs which are being increasingly used in bitches and queens. Small animal clinicians need to be aware of these compounds, their indications and contraindications as well as suggested dosage and potential side effects in dogs and cats. The use of antiemetics, particularly of peripheral dopamine antagonists such as domperidone, may help save litters of puppies and kittens.

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