

A case report on the use of domperidone for management of agalactia in a queen

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Summary

A pregnant three year old Himalayan queen was presented to Auburn University College of Veterinary Medicine with her fourth pregnancy. She had lost three previous litters of kittens within two days of birth and had a history of minimal mammary development during the peri-parturient period. Repeated sonographic measurements of fetal structures were used to determine gestational age. Six days before parturition, domperidone was prescribed at a rate of 2.2mg/kg PO q12 hours, and was continued for seven days postpartum. Parturition was uneventful and the queen's mammary development and milk production were adequate. Four weeks postpartum, three of five kittens that survived appeared healthy. Domperidone is a D₂ receptor antagonist used anecdotally for induction of lactation in small animals but the efficacy for this purpose in the queen is not well described. This case demonstrates successful induction of lactation with domperidone in a previously agalactic queen.

Keywords: Queen, agalactia, domperidone, mammary development

Background

Throughout gestation, proliferation of mammary epithelium is induced by the sex steroids 17 β -estradiol and progesterone.¹ Mammary glands begin to assume their functional secretory structure late in gestation.² Lactogenesis (production of colostrum and first milk) requires proper differentiation of secretory luminal epithelium during pregnancy. An additional requirement involves the coordinated contractions of the myoepithelial cells that surround the alveoli and duct system in order to transport secretory products.^{3,4} The essential role of gonadal, pituitary, and adrenal hormones on mammary development was investigated by Nandi in 1958.⁵ This study investigated hormone therapies using hypophysectomized, ovariectomized, and adrenalectomized mice. That work revealed that both growth hormone and estrogen are required for mammary duct development. They also demonstrated that progesterone induced side branching of the ducts, and prolactin was associated with alveolar development.⁵ The exact role that growth hormone contributes to regulation of lactogenesis and lactation in small animals remains unclear, yet it is known that progestins stimulate local production of growth hormone in the mammary gland and that mammary derived growth hormone has a stimulatory effect on mammary development.⁶ During lactogenesis, prolactin and growth hormone play a significant role in the transition from a proliferative state to a fully functional milk secreting gland.⁴

In the pregnant bitch, a rapid decline in progesterone to <2 ng/ml usually precedes parturition and occurs concomitantly with or just before a prolactin surge.⁷ This rapid decline in progesterone prior to parturition is not a prerequisite for the initiation or completion of parturition in the queen as demonstrated by Schmidt et al.⁸ In that study, seven of 12 queens had serum progesterone concentration of <1 ng/ml on the day of parturition. One queen had a serum progesterone concentration of 11.4 ng/ml on the day of parturition but had decreased to 2.6 ng/ml one day postpartum.⁸

Failure of mammary development and milk production can account for neonatal losses due to inadequate colostrum intake or starvation. Agalactia may be primary or secondary, with most cases of agalactia occurring secondary to stress induced failure of the release of prolactin from the anterior pituitary. Risk factors include systemic disease, genetic factors, environmental stressors or poor nutritional status. Treatment is directed at treating the primary cause and providing supplementation to the neonates whilst encouraging suckling to promote milk let-down. Primary agalactia may occur due to failure of endocrine mechanisms responsible for lactogenesis and galactopoiesis.⁹ A diagnosis of primary agalactia can only be made when causes of secondary agalactia are ruled out.

Disturbances of the pituitary-ovarian-mammary axis and subsequent failure of an adequate rise in prolactin could explain primary agalactia, yet the exact pathophysiology in the queen remains unclear. Despite a lack of understanding of the exact mechanisms behind this condition, there is anecdotal support for the use of antidopaminergic medications to improve lactation in the queen. Two antidopaminergic

medications currently used for lactational management in small animals are metoclopramide and domperidone. Metoclopramide is an anti-emetic agent but its antidopaminergic effects for successful induction of lactation in small animals is anecdotally reported. It antagonizes D₂-dopaminergic receptors and 5-HT₃ serotonergic receptors¹⁰ Domperidone is another oral D₂ receptor antagonist that is indicated for induction of lactation in mares with fescue toxicosis. Published reports of the use of domperidone in the dog and cat are scarce. This case demonstrates successful induction of lactation in a previously agalactic queen utilizing domperidone.

Case presentation

A two-year-old Himalayan queen was initially presented to Auburn University College of Veterinary Medicine Small Animal Theriogenology Service for a postpartum evaluation and assessment of her kittens. The queen had delivered three kittens approximately 8-12 hours before presentation. On presentation, the owner reported that kittens from two earlier litters had died within 24 hours of birth, but were not presented to a veterinary hospital. All litters were sired by the same Himalayan tom. The tom had sired other litters with no reports of neonatal morbidity or mortality. The queen was negative for feline immunodeficiency virus antibody and feline leukemia virus antigen.

The queen was clinically normal with all physical parameters within normal limits. Her mammary glands were poorly developed and milk could not be expressed from any gland. The kittens had not been observed nursing, were lethargic, cold to touch, and had yellow staining around the perineum. The queen was administered metoclopramide (0.2 mg/kg SQ q8hrs) in an effort to induce lactation. Oxytocin (1-2 IU SQ q8hrs) was administered to stimulate milk let-down. The kittens were cleaned, placed in a warmed incubator, and were administered milk replacer at a rate of 3.5ml/100mg every two hours via an orogastric tube. The sire and the dam were blood typed in order to rule out neonatal isoerythrolysis (NI) and both were found to be blood type A, thus excluding NI as a cause of the neonatal death from previous litters.

The queen and her kittens were hospitalized overnight for continued treatment. Two of three kittens died before morning and were submitted for postmortem examination. Postmortem examination of both kittens revealed moderate pleural effusion and focally extensive atelectasis. On the liver, there were small pin-point, tan-white, multifocal to coalescing nodules randomly distributed over the surface of the liver. Histopathological analysis of liver tissue showed multiple foci of lipid type vacuolar degeneration and glycogen type vacuolar degeneration. Although bacterial culture from a swab of lung tissue from one of the kittens yielded a heavy growth of *Pasteurella stomatitis*, there was no histological evidence of an inflammatory process in lung tissue. Polymerase chain reaction assay was performed on kidney and spleen tissue for detection of feline coronavirus and was negative. Postmortem findings suggested marked metabolic derangement and unknown pathology, possibly due to transient starvation but the exact etiology could not be confirmed.

For the queen, metoclopramide and oxytocin treatments were continued every eight hours for a total of six treatments, with the last two treatments being administered by the client after discharge. At the time of discharge, the one remaining kitten was nursing and the queen was showing some slight improvement in mammary development. The client was instructed to monitor maternal behavior, nursing, and to perform twice daily weight checks on the kitten. Furthermore, it was recommended that the queen undergo ovariohysterectomy based on the history of neonatal mortality and agalactia. Despite treatment, the remaining kitten died two days following discharge.

Despite recommendations to the owner to not allow breeding again, the queen was again presented six months later for a pregnancy examination. On this visit, transabdominal ultrasonography was performed and pregnancy was confirmed by visualization of multiple viable conceptuses. Using sonographic measurements of fetal and extra-fetal structures, it was estimated that the queen had been bred approximately 30 days previously. Gestational aging was performed using a combination of measurements of biparietal, abdominal, and gastric diameter.¹¹ Additional estimates were based on sonographic evidence of fetal organ maturation.¹¹ Transabdominal ultrasound was performed every seven to ten days for the remainder of the pregnancy to monitor fetal growth and viability.

Treatment

Eight days prior to the queen's estimated parturition date (six days prior to her actual delivery date), treatment with domperidone was initiated at a rate of 2.2mg/kg PO q12 hours. The queen and five kittens were presented to the University within two hours of parturition. On examination of the queen, milk could be expressed from the caudal four mammary glands. All kittens were mildly dehydrated but their body temperatures were within normal limits. Body weights ranged from 67 grams to 80 grams. The kittens appeared to have been cleaned and the dam was attentive to the kittens. Within an hour of presentation, kittens were supplemented with milk replacer via an orogastric tube at a rate of 3.5ml/100g, and warmed subcutaneous fluid [Plasmalyte[®]] was administered at a rate of 2-3ml per kitten. Serum was harvested from the sire (blood type A) and was administered to each kitten at a rate of 150 ml/kg SQ.¹²

Outcome

The queen and kittens were discharged with instructions to continue administration of domperidone to the queen at a dose rate of 2.2mg/kg PO q12 hours for an additional seven days. The owner was instructed to weigh the kittens twice daily and supplement kittens with milk replacer via an orogastric tube if the kittens failed to gain weight. Following discharge, the weakest and smallest two kittens failed to thrive and required additional supplementation. Despite treatment, both died at home within the first week of life. A necropsy was not performed so the cause of death could not be determined. The surviving three kittens did not require additional supplementation following discharge. Four weeks following discharge, the remaining three kittens were growing, appeared healthy, and were transitioning to solid food. Further communication with the owner revealed that the three remaining kittens survived and at eight weeks of age, were placed into adoptive homes.

Discussion

Agalactia is reported occasionally in queens but the true prevalence of this condition remains unknown. The relative role of reproductive hormones, prolactin, and growth hormone in mammary development is likely species dependent.¹³ This species specific variation is important because the medications and doses currently used for induction of lactation in small animals are extrapolated from both human and large animal studies.

In domestic mammals, prolactin is secreted by the anterior pituitary and is under inhibitory control by the hypothalamus, mediated in part by dopamine.¹⁴ In addition to its role in mammogenesis, lactogenesis and lactation, it also plays a central role in the development of maternal behavior.¹⁵ In the queen, prolactin production starts to increase around day 35 of gestation.¹⁶ It reaches a plateau around the third and fourth week of gestation and then gradually declines. It rises again relatively abruptly to 39-48 ng/ml a few days before parturition.^{8,16,17}

The dopamine neurons that control prolactin secretion are located in the hypothalamus. They act as a synchronous network to release dopamine into the pituitary portal system in a pulsatile or phasic fashion.¹⁸ Hypothalamic control of prolactin secretion differs from other pituitary hormones in that it is primarily inhibitory.¹⁸ Dopamine acts on D₂ receptors in the pituitary gland to inhibit lactotrophs. A unique feature of lactotrophs is that they display spontaneous electrical activity in the absence of dopaminergic activity and calcium influx stimulates prolactin secretion.¹⁸ Dopamine exerts its effects by inhibiting calcium influx and induces a state of membrane hyperpolarization. The regulation of dopamine neurons is via a short feedback loop where prolactin itself stimulates hypothalamic dopamine synthesis.¹⁸ During pregnancy and early lactation, dopamine release from the hypothalamus reduces so that prolactin secretion remains high.¹⁸

A clearer understanding of the pathophysiology of primary agalactia in the queen is needed. Knowing the unique species specific regulators of lactogenesis and galactogenesis would guide management of this condition. It is likely that primary agalactia has multiple etiologies which have complex interactions. Much of the current research in mammary responses to prolactin in small animals revolves around identification of markers for mammary neoplasia.^{19,20} Interestingly, the observed initial

rise in prolactin that occurs during pregnancy occurs relatively concomitantly or just after a rise in placental relaxin.²¹ Placental relaxin is a peptide hormone that is first detectable in plasma of the pregnant queen between days 20 and 25 of gestation. Concentrations increase and reach a plateau by days 30-35 and then decline in the last 10-15 days of gestation.²¹ Studies investigating the association between mammary development and relaxin have produced conflicting data. Some research supports a role of relaxin in mammary development while others do not support an association. A study by Zhao et al. demonstrated that relaxin deficient mice were unable to develop mammary tissue. Pups were unable to suckle and died within the first 24 hours of life.²² In contrast, more recent studies revealed that relaxin does not play a significant role in mammary development. Mice with targeted gene deletion for relaxin or its receptor (Rxfp1) had normal mammary development, evidenced by an absence of morphological or phenotypical defects in the lobuloalveoli or ductal system of the mammary gland during late pregnancy or early lactation.²³ Furthermore, a very recent study revealed that nipple size and lactation were normal in Rxfp1 knockout mice.²⁴

The anti-dopaminergic effect of metoclopramide has been utilized for lactation management in both small animals and women. It was originally marketed in Europe as an antipsychotic for humans, and later in the United States as a gastrokinetic.¹⁴ Its use for induction of lactation in the bitch and queen is anecdotal. Romagnoli et al. reviewed current protocols in small animal veterinary medicine and reported ranges as low as 0.2-0.5 mg/kg SQ or PO twice or three times daily, to higher doses ranging from 1-5 mg/kg SQ or PO up to four times daily.⁹ Administration of metoclopramide results in a subjective improvement in milk production in at least 50% of cases.⁹ There is no clear dose dependent relationship with efficacy, although high doses have been associated with extrapyramidal signs in canines and should therefore be avoided.⁹

Oxytocin is frequently used alone or in combination with metoclopramide for treatment of galactostasis and can be used at doses of 0.5 to 1 IU IM 15-20 minutes before nursing.²⁵ In this particular queen, administration of metoclopramide and oxytocin had only a minimal effect on milk production and milk let down.

Domperidone was first developed as an antiemetic agent in humans. It was withdrawn from the human market following the observation of cardiac arrhythmias in patients who were receiving very high doses when used concurrently with chemotherapy. It is still used widely in Canada and Europe for lactational management in women.⁹ In veterinary medicine, it is labeled as Equidone[®] Gel (Dechra Veterinary Products, Overland Park, KS) and is used to treat agalactia associated with fescue toxicosis in periparturient mares.²⁶ The drug is administered orally at a dose of 1.1 mg/kg once daily starting 10 to 15 days prior to the expected foaling date. Treatment is continued for up to five days postpartum.²⁶ There are anecdotal reports that domperidone is effective at improving milk yield in small animals at doses of 1.5-2.0 mg/kg in the queen and 2.2 mg/kg in the bitch.⁹ The most commonly reported side effect in the bitch is diarrhea.⁹

To our knowledge, this is the first publication reporting the use of domperidone for induction of lactation in the queen. The apparent improvement in treatment response to domperidone rather than metoclopramide may be attributable to the differences in pharmacological behavior of the two drugs. While both metoclopramide and domperidone increase prolactin by inhibition of dopaminergic activity, a notable difference between the two drugs is that the latter does not readily cross the blood brain barrier.²⁷ Domperidone acts on peripheral D₂-dopaminergic receptors, and therefore offers the advantage that it is less likely to cause extrapyramidal signs when compared with metoclopramide.²⁷ Alternatively, had drug therapy using metoclopramide been initiated prepartum, as was domperidone, treatment response in this queen may have been equal or better. Serial measurement of endogenous prolactin, and perhaps relaxin, could have provided valuable insight to this observation.

Two of the five kittens failed to survive despite treatment and supplementation with milk replacer. Since these kittens died at home and necropsy was not performed, the cause of death could not be determined. The owner was performing the supplemental feedings as directed by clinicians during daily phone conversations. Both kittens failed to gain weight, became progressively weaker, and died during the night when supplemental feedings were more sporadic. Starvation is not likely a cause of

death in these two kittens if the owner was complying with the scheduled feedings. Underlying pathology of the gastrointestinal tract or other system is more likely, but since no necropsy was performed, cannot be ruled in or out as a cause of death. Therefore, when treating agalactia in the mother, care should be taken to fully assess kittens for any signs of other pathology and rule out other common causes for neonatal loss.

Domperidone administered orally at a rate of 2.2mg/kg BID initiated approximately one week prior to parturition and continued for seven days postpartum was successful for induction of lactation in a previously agalactic queen, and was not associated with negative side effects. Further research is warranted regarding exact dose, efficacy and toxicological effects.

Learning points

- The pathogenesis of primary agalactia in the queen remains to be elucidated.
- Current, published estimates of sonographic measurements of fetal maturity are useful to time protocols for lactation induction in the queen when breeding dates are not known.
- Domperidone is a reasonable option for induction of lactation in the queen.

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