Leuprolide Acetate

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Leuprolide acetate is a potent Gonadotropin Releasing Hormone (GnRH) agonist. The general premise behind leuprolide is that it inhibits the synthesis of lutenizing hormone and follicle stimulating hormone via a negative feedback. By reducing the production of these hormones, the drug effectively reduces estrogen and androgen production. This compound has been formulated as a depot formulation (1-, 3- and 4-month) to provide long-term treatment for reproductive diseases in humans, including mammary and prostatic cancer, endometriosis, and precocious puberty.[1] In these formulations, the hydrophilic leuprorelin is held in biodegradable highly lipophilic synthetic polymer microspheres.[2] The depot is released over a defined length of time depending on the polymer. In humans, peak plasma concentrations can occur rapidly (1-3 hours) following a subcutaneous injection, and the microspheres help maintain plasma concentrations (1-month depot) between 0.4 to 1.4 μg/L for almost a month.[2] The long-term use of this drug in humans has been found to desensitize the pituitary. Leuprolide acetate is not recommended during pregnancy, as it can cause fetal abnormalities.

Although formulated for humans, leuprolide acetate has been used fairly extensively in exotic and avian species. In exotic animal practice, this compound is primarily used to manage adrenal gland disease in ferrets and excessive egg laying in psittacines. However, this compound has also been used to induce molting in chickens, stimulate rat spermatogenesis, and serve as a reversible contraceptive in wapiti (*Cervus elaphus nelsoni*).[3-5] The author also has some anecdotal success using leuprolide acetate (0.15 mg/kg q 4 weeks) as a method of reducing aggression in intact male green iguanas (*Iguana iguana*). Because the husbandry methods used to manage captive exotic species have improved over the past decade, many of these animals are living longer and successfully reproducing. These captive successes have led to the development of new and challenging health crises for the veterinarian to manage. The purpose of this article is to provide a review of some common problems that veterinarians may encounter with exotic species that may be managed with leuprolide acetate.

Adrenal gland disease is the most common presentation for ferrets greater than 3 years of age at the Louisiana State University School of Veterinary Medicine. Affected ferrets frequently present with a history of bilaterally symmetric to generalized alopecia and pruritis. The skin of affected animals is often smooth and appears "thin." Vulvar swelling is a common finding in females, while prostatic enlargement, urethral obstruction, and dysuria are common in males. A return to sexual activity and aggression are occasionally observed in the males. Anemia or pancytopenia may also occur. Histopathology of affected glands often reveals hyperplasia, benign adenoma, or adenocarcinoma. The etiology of this disease process is unknown. However, early-age neutering and extended photoperiod have been implicated.[6,7] Neutered ferrets with adrenal gland disease frequently produce sex hormones from the adrenal cortex, including 17 α-hydroxyprogesterone, androstenedione, and dehydroepiandrosterone sulfate. The production of the sex hormones has been attributed to the chronic stimulation of the adrenal gland by lutenizing hormone and follicle stimulating hormone.[8]

Current treatment recommendations for adrenal gland disease in ferrets include both surgical and medical options. Given a choice between the two different treatment options, the surgical option is preferred because it is more likely to be curative.

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However, surgery may not be possible in cases where the animal is not stable (eg, pancytopenia). Surgery also may not be an option in cases where the adrenal gland has metastasized into the vena cava or other visceral organs. In these cases, medical management is preferred. Wagner and coworkers[9] evaluated the efficacy of leuprolide acetate as a method to medically manage adrenal gland disease in ferrets. The authors found that a single intramuscular injection of leuprolide acetate (100-150 μg/kg) was effective at alleviating the clinical signs associated with adrenal gland disease. In the majority of the treatment ferrets, the pruritis, vulvar swelling, and prostatic cysts had resolved within 2 weeks of treatment, while hair regrowth was evident within 4 weeks of treatment. This author has found that a single injection (100 μg/kg) of the 3.75 mg depot every 6 weeks is effective at preventing the recurrence of clinical signs in ferrets. Clients should be made aware of the fact that treatment with leuprolide acetate is only palliative, and that those cases with malignant tumors may continue to metastasize.

Reproductive disorders are a common problem in captive psittacines. To better interpret the physiologic response of a bird with a reproductive disorder, it is important to have a basic understanding of how hormones cycle in birds. Serum sex steroid levels in captive psittacines can vary during the different stages of reproduction.[10] In Orange-winged Amazon parrots (*Amazona amazonica*), testosterone levels in males were highest during nest box inspection, but declined during the parental stages of egg management.[10] In females, estradiol levels were highest during the egg-laying season. Changes in progesterone levels between the different stages of reproduction were less dramatic; however, male progesterone levels were higher than female levels. Understanding the cycle of these hormones is important when considering therapeutic plans to control reproductive disorders in captive psittacines.

The production of lutenizing hormone in captive psittacines can be affected by the provision of nesting areas, photostimulation, and mate interaction.[11] However, in some species, such as cockatiels (*Nymphicus hollandicus*), lutenizing hormone levels can increase spontaneously. It is not uncommon for cockatiels to be presented to veterinarians with a history of chronic egg laying. Many of these birds are housed individually, not provided a nest box, and receive no natural sunlight. Affected animals may lay large numbers of eggs, and deplete their calcium stores. If left untreated, birds may develop muscle fasiculations and life-threatening seizures. The current methods used to control chronic egg laying are the regular use of leuprolide acetate or a hysterectomy. The hysterectomy is the preferred treatment method because it eliminates the chance for recurrence. However, the surgical approach is not without risk. In addition, many veterinarians are not comfortable performing this surgery on small psittacines.

Leuprolide acetate may be used to decrease lutenizing hormone levels by down regulating GnRH receptors.[12] The depot formula is rather expensive, but the volumes required for these birds are quite small. Recommended doses are also quite varied. Millam and Finney[12] evaluated the efficacy of a 3.75 mg leuprolide acetate depot on egg laying in cockatiels. Leuprolide acetate was administered at a dose calculated to achieve a daily release rate of 17, 52, or 156 μg/mL/kg/d. A control group received only the vehicle. The authors found that a single injection of leuprolide acetate was effective at reversibly preventing egg laying in cockatiels for 12 to 19 days; however, there was no significant difference in nest inspection or bowl formation. Although the depot formulation has a 28-day effect in humans, it was limited in the birds. The authors concluded that the difference noted in the study may have been attributed to the small dosing volume given to the birds or the higher body temperature and metabolism of the birds.

Currently, there is a wide range of published leuprolide acetate doses (100-800 μg/kg) for managing captive psittacines with hormonal imbalances.[13] This author has found that 400 μg/kg is generally effective at managing cockatiels with chronic egg-laying problems. In addition to the leuprolide treatment, clients are told to remove any materials that might be perceived by the bird as nesting materials, and photostimulation is limited to 10 hours per day. Because cockatiels are indeterminate layers, eggs should not be removed after they are laid.[14] Removal of the eggs may stimulate the bird to lay additional eggs, which may further complicate calcium homeostasis.

In the commercial poultry industry, the opposite problem exists. As chickens age, there egg production decreases. This reduction in egg production can be partially reversed when a chicken molts. The exact physiologic reason for this change is not known. However, the poultry industry has found that by forcing chickens to molt they can increase egg production. Historically, chickens are forced to molt by food deprivation. Because this is considered cruel and inhumane by animal welfare groups, researchers have been interested in pursuing novel methods to induce a molt in a chicken. Dickerman and coworkers[3] found that leuprolide acetate given to chickens

at a daily dose of 60 μg/d for 14 days led to ovarian regression. In addition to inducing the cessation of egg laying, the chickens also molted. Burke and Attia[15] found similar results using a single intramuscular injection of leuprolide. The chickens given leuprolide also were found to return to egg laying faster than those birds that were food deprived. Although not evaluated in captive psittacines, leuprolide acetate may prove useful in the management of breeding animals.

Conclusions

Leuprolide acetate has been found to be very useful as a method to control both adrenal gland disease in ferrets and chronic egg laying in psittacines. It is likely that this drug may have additional value in regulating hormone production in other exotic species too. Future research to evaluate its effectiveness in controlling androgen production in animals with male aggression, such as green iguanas, should be pursued. In addition, the drug may also prove invaluable as a reversible contraceptive for exotic species.

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