GnRH Agonists in Avian and Exotic Patients: Opportunities and Challenges

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Abstract: Gonadotropin-releasing hormone agonist (GnRHa) peptide drugs including leuprolide and deslorelin have been successfully used for decades in humans, domestic animals, free-ranging wildlife and animals in zoological facilities, and more recently in avian and exotic companion animals. Typical uses for GnRHAs include reproductive stimulation, reproductive suppression (contraception or hormone-responsive disease suppression), and control of aggression. Species respond differently to various GnRHa medications, in part due to taxonomic differences in neuroendocrine physiology but also due to differences in drug formulation. The decision of which GnRHa to prescribe in a particular patient depends on the patient’s species physiology, the intended purpose (eg, reproductive stimulation versus suppression), the desired duration of effect, legal restrictions, and product availability/cost. For avian and exotic companion animal patients in the United States, leuprolide (depot form) is a GnRHa option that is expensive, but legal for extra-label use in a broad variety of species. In contrast, deslorelin is less expensive, but is frequently unavailable, and its use is prohibited in pets other than ferrets with adrenocortical disease.

Neuroendocrine Physiology Related to GnRH Agonists

The hypothalamus, anterior pituitary gland and gonads are the most important organs involved in the pharmacodynamics of GnRHAs.1 Normally, specific neurons in the hypothalamus produce pulses of endogenous gonadotropin-releasing hormone (GnRH), which is transported via the hypophyseal portal system to the anterior pituitary gland and bound by GnRH receptors there, causing the anterior pituitary to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH) into the systemic circulation. Despite their female-based names, FSH and LH have effects in both females and males. In testes, FSH stimulates Sertoli cells to produce nutrients necessary for spermatogenesis and LH stimulates testosterone production by Leydig cells, which then supports spermatogenesis. Testosterone also targets many tissues outside the testes, including those responsible for sex-specific secondary characteristics, as well as the regions of the brain that mediate aggression, territoriality, courtship and mating.2 In ovaries, FSH stimulates follicles to produce estradiol, which causes changes throughout the body (eg, vaginal mucus consistency, vulvar appearance, sex skin coloration) as well as inducing estrous behavior. Once serum estradiol concentrations become high enough, feedback to the hypothalamus causes a pulse of GnRH to be released, and this causes an LH surge, which causes ovulation to occur. As the ruptured follicle luteinizes, progesterone is produced. This is an example of a positive feedback loop which exists between hormone production in the gonads (estradiol, progesterone, testosterone) and hypothalamic GnRH release. Negative feedback loops also exist between all components of the hypothalamic-pituitary-gonad axis; for example, high serum concentrations of estradiol, progesterone or testosterone cause the hypothalamus to release less GnRH, avoiding overstimulation of target tissues.
Endogenous release of GnRH occurs in a pulsatile fashion, not a continuous one, and it is this pulsatile release that contributes to the stimulatory effect of GnRH. As the term “agonist” would suggest, the effect of synthetic GnRHa is initially that of stimulation, but in contrast to endogenous GnRH, ongoing non-pulsatile release of the GnRHa drug from an injection site or long-acting implant causes down-regulation of GnRH receptors in the anterior pituitary and elsewhere, resulting in a significant decrease in LH, FSH and therefore testosterone, estradiol and progesterone production. Synthetic GnRHa also have a higher affinity for GnRH receptors and a longer half-life in systemic circulation compared to natural GnRH, which makes suppressive effects of GnRHa more likely at lower doses and for longer periods of time than natural GnRH. Increasing the dose of GnRHa administered may result in a longer duration of suppressive effect, assuming similar formulations are used; this may be because with a higher dose of agonist, the release rate can be maintained above a critical threshold for down-regulation for a longer period of time, or it may be that the pituitary takes longer to recover from exposure to higher doses of agonist. Clinical uses of GnRHa relate to their stimulatory (with short-acting drug formulations) or suppressive effects (with longer-acting formulations). In humans, GnRHa are approved for suppressive purposes, including those which facilitate the timing of assisted reproductive techniques (eg, suppressing a premature LH surge before exogenous stimulation of ovulation is performed) or those related to hormone-responsive conditions (eg, prostatic cancer, endometriosis, uterine leiomyoma, central precocious puberty).

Although the clinical intent is often to suppress hormone-related disease, one must consider the consequences of an initial stimulatory “flare” phase, and ways to mitigate these consequences. In females, the initial stimulation may result in an induced estrus cycle, and in males a temporary increase in circulating testosterone. In female carnivores (eg, dogs, cats, wolves), administration of an oral short-acting progestin such as megestrol acetate is recommended for 1 week before and 1 week after deslorelin implant placement, to prevent the flare phase that might otherwise occur with GnRHa; this recommendation has resulted in fewer pyometra cases in treated carnivores.

It is important to realize that many organs other than reproductive ones may contain GnRH receptors (eg, adrenal glands, pancreas, heart, liver, larynx, colon, skin, brain), therefore down-regulation of GnRH receptors may cause multi-organ adverse effects in addition to those involving the reproductive system. Human patients treated with GnRHa for prostatic cancer show a higher incidence of cardiac disease, for example. However, 6 and 12 month implants of Suprelorin have been shown to be safe in domestic dogs, and are approved for use in Europe, Australia and New Zealand.

The effects of GnRHa are typically reversible with time, although the length of time to reversal is highly variable and unpredictable between species and between individuals, and not necessarily correlated with the dosage received or duration of treatment. If more immediate reversal is desired in a deslorelin-treated patient, the implant may be surgically removed using ultrasound guidance and a 18 MHz transducer, although this can be difficult due to the implant’s small size and friability.

Vaccines are available against GnRH, and they give the advantage of not inducing an initial stimulation phase as GnRHa might. These vaccines have been used successfully to suppress ovarian activity in Asian elephant (Elephas maximus), mares, prairie dogs and deer. However, GnRH vaccines are formulated with adjuvant, in some cases must be given with multiple booster doses, and elicit variable responses in individual patients, making this technology less feasible for many veterinary applications.

Synthetic peptide GnRH antagonists (eg, ganirelix, cetrorelix, abarelix) are available as implants and injectable formulations in addition to GnRHa, and their effect is to block the action of endogenous GnRH by blocking the GnRH receptors in the pituitary gland. Non-peptide antagonists are also being developed. These GnRH antagonists would be assumed the more logical selection for hormone suppressive benefit than GnRHa, however they are considerably more expensive and shorter acting than the agonists, which limits their application to critical patients in which rapid effect is needed.
GnRH agonist use in domestic animals including ferrets

Deslorelin is available in an oil-based injectable form which is approved by the US Food and Drug Administration (FDA) for induction of ovulation in mares (SucroMate Equine, deslorelin 1.8 mg/ml, Thorn BioScience, Louisville, KY 40204, USA), or in implant form for the same purpose (Ovuplant, deslorelin 2.1 mg implant, Dechra, Shropshire SY4 4AS, UK). These formulations are short-acting, therefore a suppression phase does not occur after the intended initial stimulation phase. In the US, deslorelin is legally marketed as an Indexed Product by the FDA under minor species index file 900-013 for use in ferrets with adrenocortical disease (Suprelorin-F, deslorelin 4.7 mg implant, Virbac Animal Health, Inc., Fort Worth, TX, USA). Adrenocortical disease (hyperadrenocorticism) is common in ferrets in the US, likely due to a combination of factors including genetic predisposition, early-age gonadectomy (which removes gonadal negative feedback on endogenous GnRH production by the hypothalamus) and abnormally long photoperiods.5 After a 3 mg or 4.7 mg deslorelin implant is placed subcutaneously in an adult ferret with clinical signs of adrenocortical disease (eg, alopecia of caudal body and tail, pruritus, vulvar swelling, prostatomegaly), clinical signs improve within 2-4 weeks and palliative benefit lasts for 3-30 months without an apparent initial stimulation phase.5 Availability of deslorelin implants (Suprelorin-F or Suprelorin) has been unreliable however, due to manufacturing and shipping issues.

Prior to Suprelorin being made commercially available, the depot injectable suspension form of leuprolide (Lupron Depot 1-month, TAP Pharmaceuticals, Deerfield, IL 60015, USA) was used for a similar purpose in ferrets (100-200 µg per ferret), with a similar timeframe for improvement of clinical signs (2-4 weeks) but much shorter duration of efficacy (1.5-8 months). The same product was also used at a dosage of 100 µg/kg IM for treatment of a ferret with hyperaldosteronism due to an adrenocortical adenoma. Some veterinarians believe that there are individual ferrets which respond better to depot leuprolide than to deslorelin, in contrast to most published information. Dosing recommendations for leuprolide in ferrets with adrenocortical disease include 100-200 µg of the 1-month depot form of leuprolide per ferret IM once a month, with higher doses being required with time. Other depot formulations of leuprolide (3-month, 4-month) may be used for slightly longer durations of effect. Leuprolide injectable is currently available in the US in a non-depot form (Leuprolide 5 mg/ml, Teva Pharmaceuticals USA, Inc., Sellersville, PA 18960, USA) which is relatively inexpensive (approximately $115 per 2.8 ml vial), however this formulation is short-acting therefore will only cause hormonal suppression with daily (instead of monthly) injections. The multi-dose vial form of leuprolide depot suspension is not currently available in the US; the depot form is instead available as a two-part syringe manufactured for one-time injection (Lupron Depot 1-month, leuprolide 3.75 mg, Abbvie, North Chicago, IL 60064, USA), which makes repeated treatment of small patients cost-prohibitive (over $1100 per syringe).

Other domestic species where GnRHa-induced hormonal suppression has been demonstrated include dogs, cats, female cattle and rats. In the European Union, deslorelin implants (Suprelorin, Virbac S.A., 06516 Carros, France) are marketed for contraception of male dogs and male ferrets, with a 4.7 mg implant being recommended for 6 months of effect in dogs and the 9.4 mg implant being recommended for 12 months of effect in dogs or 16 months in ferrets. In male rats, either a 25% segment of a Suprelorin 4.7 mg implant or a full 9.4 mg implant causes testicular size to decrease (indicating reproductive suppression) for at least 8 months.

GnRH agonist use in zoological facilities and free-ranging wildlife

Although Suprelorin use in the US is prohibited in companion animals other than ferrets with adrenocortical disease, it can be used legally in US zoological facilities accredited by the Association of Zoos and Aquariums (AZA) as an Investigational New Animal Drug, part of an AZA-coordinated research trial.4 Zoo-housed animals tend to have long lifespans and captive housing space is finite, with breeding recommendations changing over time, therefore reversible/temporary contraception is an integral management tool in zoos. To date, over
260 species have been treated under this AZA program with deslorelin implants for the purpose of temporary contraception, including elasmobranchs, reptiles, tamandua, tree shrew, anteaters, hyrax, perissodactyls, artiodactyls, pinnipeds, cetaceans, carnivores, bats, birds, marsupials, lemurs, monkeys, apes and rodents.

Depot leuprolide has been used for male-based contraception in several marine mammals. However, suppressive effects including contraception and aggression control have been difficult to achieve in male artiodactyl patients (eg, cattle, deer, antelope) using GnRHa. In these species, GnRHa treatment succeeds in blocking the pulsatile but not basal secretion of both LH and testosterone (and LH production may actually increase over time), with the result that enough testosterone is present to support both spermatogenesis and male behavior. Male marsupial patients have also appeared refractory to GnRHa effects.4

Long-acting deslorelin implants have been used successfully for aggression control or testosterone suppression (for behavioral purposes) in zoo felids, canids, sea otters and macaques.6 Depot leuprolide has been used for aggression control in bachelor groups of California sea lions (Zalophus californianus), sea otters, and in a male Asian elephant housed in close proximity to circus handlers. Luteinizing hormone-releasing hormone (triptorelin) was used successfully in wild male Hawaiian monk seals to suppress testosterone production.

In contrast, short-acting deslorelin has been used in injectable and implant forms to induce estrus and ovulation in rhinoceros, contributing to the first successful production of a rhinoceros embryo in vitro.

**GnRH agonist use in companion avian and exotic patients (herptiles, rodents, rabbits, birds)**

Depot leuprolide has been used in companion avian and reptilian patients for many years, for suppression of hormone-related behaviors and disease. Aggression control using depot leuprolide has been attempted in male green iguanas with variable success, and more successfully in a rabbit with hypertestosteronism due to adrenal neoplasia. However, depot leuprolide’s high cost and relatively short efficacy have driven veterinarians to seek alternatives for hormone suppression therapy.

Legal use of Suprelorin in zoos and research facilities, as well as use in other countries, has generated many published articles, conference presentations and listserve discussions in support of deslorelin implant use for various species and purposes. Reported uses of deslorelin implants in companion animals other than domestic dogs, cats or ferrets include aggression control in male bearded dragons,7 treatment of cystic ovaries in guinea pigs, non-surgical contraception for rodents and prevention of mammary fibroadenomas in rats (S. Mitchell, written communication, March 2013). In birds, long-acting leuprolide or deslorelin have been used in patients with reproductive disease, for behavioral issues suspected to have a hormonal component, as well as for elective purposes (eg, induction of molt to reset egg-laying seasonality). Efficacy of GnRHa in avian patients has been quite variable. Among galliform and columbiform species, 1-2 years of egg-laying suppression was achieved in chicken hens (Gallus gallus) after administration of a 4.7 mg or 9.4 mg Suprelorin implant, but a 4.7 mg Suprelorin implant caused only 2-12 weeks of egg-laying suppression in Japanese quail (Coturnix coturnix japonica) of much smaller body size,8 and a decrease in egg-laying for 7 weeks in pigeons (Columba livia). In birds, similar to other taxa, depot leuprolide treatment appears to have a much shorter duration of benefit than deslorelin. Hispaniolan Amazon parrots (Amazona ventralis) given injections of depot leuprolide showed hormone suppression for just 2 weeks, and cockatiels (Nymphicus hollandicus) showed suppression of egg-laying for approximately 1 month.9 Mallard ducks (Anas platyrhynchos), black ducks (Anas rubripes) and pigeons (Columba livia) given depot leuprolide showed no evidence of reproductive suppression. Environmental cues such as mate presence, nestbox presence, seasonality (breeding season versus nonbreeding season), nutrition and photoperiod are hypothesized to be strong influences on reproductive activity in birds, counteracting the physiologic effects of GnRHa treatment.10
In contrast, shorter-acting GnRHa have been useful for reproductive stimulation. Synthetic luteinizing hormone releasing hormone has been used for induction of breeding in many species of frog. Lecirelin injectable, administered transcutaneously as a compounded formulation in moisturizing cream, encouraged an earlier onset of egg laying in canaries (*Serinus canaria*). Buserelin injectable was compounded into a silicone material to form an implant, then injected subcutaneously using a 24 ga needle into budgerigars (*Melopsittacus undulatus*), which resulted in stimulation of egg-laying and higher fecal concentrations of testosterone and estradiol. Buserelin injectable itself (without implant formulation) was administered to male cockatiels and sulfur-crested cockatoos (*Cacatua galerita*) to successfully induce testosterone release.

The incidence of adverse effects related to GnRHa use in avian and exotic patients appears to be low, with just one report of suspect anaphylaxis to repeated leuprolide depot suspension injections in elf owls (*Micrathene whitneyi*).

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**References**


