Estrus Suppression in Dogs

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KEYWORDS

• Agonist • Androgen • Antagonist • GnRH • Hormonal downregulation
• Progestogen

KEY POINTS

- Although progestogen administration is the most commonly used method of estrus suppression in dogs, there has not been and it is unlikely there will be a universally safe or effective progestogen in dogs.
- Continuous treatment with androgens for up to 5 years has been demonstrated, but it is generally not recommended to treat continuously for more than 24 months.
- Following an initial flare-up in gonadotropin concentrations, sustained exposure to gonadotropin-releasing hormone (GnRH) agonists reduces gonadotropin secretion through GnRH receptor downregulation, internalization, signal uncoupling, and a decrease in GnRH receptor expression.
- GnRH antagonists directly block pituitary GnRH receptors resulting in immediate suppression of gonadotropin release without a flare-up, but currently available products are too short-lived to be clinically beneficial.

INTRODUCTION

Within the United States, suppression of the canine estrous cycle is predominately attained by surgically removing the ovaries (ovariectomy) with or without the uterus (ovariohysterectomy). However, not all owners have their pets surgically sterilized. For purpose-bred bitches, the safest and most effective and least expensive method to prevent unwanted pregnancy is indoor confinement and segregation from intact males. For those bitches not intended for breeding, pet owners may still be reluctant to consider traditional surgical sterilization given recent (albeit confounding) evidence of long-term health problems associated with gonad removal, including obesity,

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urinary incontinence, endocrine disorders (eg, hypothyroidism, diabetes), musculoskeletal disorders (eg, cranial cruciate ligament rupture, hip dysplasia), behavioral disorders (eg, aggression, fear) and cognitive dysfunction, and neoplasia (eg, osteosarcoma, hemangiosarcoma, mastocytoma, lymphoma).

There are numerous nonsurgical methods for estrus suppression that have been used previously and that are currently being used. Pharmacologic methods of estrus suppression must be safe, reliable, and reversible. Hormonal treatments using reproductive steroid hormones (progestogens or androgens) or gonadotropin-releasing hormone (GnRH) analogues result in negative feedback, effectively shutting down the hypothalamic-pituitary-gonadal axis.

PATIENT EVALUATION OVERVIEW

Indications for suppressing estrus for bitches intended for future breeding include inconvenient timing of estrus for owner (American Kennel Club [AKC] performance classes prohibit exhibition of bitches in season) and long-term medical management of pyometra. For bitches not intended for breeding and when surgical sterilization is not an option, estrus suppression is important for prevention of pregnancy. Commercially available options in the United States for estrus suppression in dogs have declined over the last 3 decades, although most are still available through veterinary compounding pharmacies. Estrus-suppression protocols mediate their action by inhibiting pituitary gonadotropin secretion and release, mainly that of luteinizing hormone (LH). These protocols include the use of progestogens, androgens, GnRH agonists, or GnRH antagonists. Because LH is luteotropic in the dog, administration of estrus-suppression drugs to pregnant dogs may result in abortion and/or fetal urogenital malformations (eg, hypospadias in males, masculinization in females). Practitioners should first confirm that patients are not pregnant or that their owners know about and are ready to accept the consequences.

PHARMACOLOGIC TREATMENT OPTIONS FOR ESTRUS SUPPRESSION

Progestogens

Canine estrus suppression using progestogens has been practiced for many decades with the first report by Murray and Eden[1] in 1952. The mechanism of the estrus suppressive activity of progestogens in dogs is still unclear. In many species, there is evidence that progestogens reduce serum concentrations of gonadotropins. However, high doses of medroxyprogesterone acetate (MPA) or megestrol acetate (MA) administered to ovariectomized beagle bitches for several months did not reduce the increased circulating concentrations of LH nor did it lower LH concentrations in intact bitches.[2,3] On the contrary, basal plasma follicle-stimulating hormone (FSH) and LH concentrations increase during the first months of MPA treatment,[4] which may be due to a direct inhibitory effect of MPA at the ovarian level, resulting in suppression of the ovarian secretion of estradiol or inhibin.[5,6]

MPA (Depo-Provera) is a long-acting injectable progestin that was labeled for estrus suppression in the bitch (Promone).[7] MPA may be administered as a single subcutaneous injection (2 mg/kg; maximum 60 mg per animal)[8] or orally (5 mg once daily [10 mg for large dogs during the first 5 days]) for a maximum of 21 days.[9] Delmadinone acetate is similar to MPA and is used to postpone estrus.[10] MA has been used extensively for temporary estrus suppression in the bitch and is rapidly metabolized when given orally.[11] When given at a daily dose of 2.2 mg/kg body weight orally for 8 days beginning in early proestrus, estrus was suppressed in 92% of cases.[12] Two- to 4-week administration of MA during anestrus alternating with an untreated

period of 3 to 4 months is also effective. Chlormadinone acetate 2 mg orally once a week[13] or (0.5 mg/kg, n = 2) orally for 8 days is equally effective as MA.[14] Proligestone is commercially manufactured in Europe (Delvosteron) and is labeled for estrus suppression (10–30 mg/kg subcutaneously repeated at 3 and 7 months following the initial injection).[15]

All of these drugs should be administered during anestrus approximately 1 month before the expected onset of the next estrous cycle. The first estrus after the use of proligestone can be expected in most bitches within 9 to 12 months but may take up to 2 to 3 years. With respect to MPA, the return to estrus may vary from 2 to 9 months.[9] It is important to note the subcutaneous contraceptive implants labeled for human use containing levonorgestrel (Norplant) do not suppress estrus in dogs.[16]

Although progestogen administration is the most commonly used method of estrus suppression in dogs,[17] there has not been and it is unlikely there will be a universally safe or effective progestogen in dogs. Reported adverse effects depend on the type of progestogen administered, dose, treatment duration, and age of the animal.[18,19] The most commonly reported adverse effect is increased appetite leading to weight gain, lethargy, or restlessness.[4,11–13,20] Progestogens have a moderate affinity for the glucocorticoid receptor[21] and can result in clinical signs consistent with adrenocortical suppression (eg, alopecia, hair discoloration, thinning of the skin).[22] Progestogens can also cause acromegaliclike symptoms, including hypertrophy of skin and other soft tissues and overgrowth of some bone and cartilage, occurring in response to progesterone-induced hypersecretion of growth hormone by mammary tissue as well as the pituitary, and resulting in increased serum concentrations of insulinlike growth factor 1.[23] Elevations in serum progesterone can also cause diabetic insulin resistance, acting either directly or via increased growth hormone production.[24–27] This hypersecretion of growth hormone as a result of progestogen administration can be successfully treated by the progesterone receptor blocker aglepristone.[28]

The next most significant adverse effect reported are uterine pathologic conditions, with the prevalence of cystic endometrial hyperplasia-endometritis as high as 45%.[29–31] Pyometra developed in 0.8% of bitches treated with progestogens.[12] It is important to note that the canine mammary gland produces pathologic changes following progestogen administration in a way that is not seen in other species.[32,33] Apparently a significant level of constitutive expression of progesterone receptors occurs in canine mammary tissues.[23] Unlike laboratory animals, progestogen administration induces progesterone receptor synthesis in the canine mammary gland.[34] In addition, the dog seems to have a unique sensitivity to the mammary tumor-promoting effect of progestogens via progestin-induced growth hormone induction.[35] Progestogen-induced neoplastic transformation of mammary tissue starts with the proliferation of undifferentiated terminal ductal structures,[36] leading to hyperplasia, adenomatous changes, and eventually adenocarcinoma.[23,26,27,31,37]

Androgens

Androgens have also been used for canine estrus suppression. Mibolerone is a synthetic androgen that was commercially manufactured (formerly sold under the name of Cheque Drops) and labeled for estrus suppression in dogs.[17,38,39] The dose for mibolerone varies in bitches depending on body weight and breed.[11] For bitches up to 12 kg, the mibolerone dosage is 30 μg/d. For bitches 12 to 23 kg, the mibolerone dosage is 60 μg/d. For bitches 23 to 45 kg, the mibolerone dosage is 120 μg/d. For bitches more than 45 kg, the mibolerone dosage is 180 μg/d. Any German shepherd dog or any Alsatian-derived mixed breed should receive the maximum daily dosage (180 μg/d). The reason for the higher dosage requirement within Alsatian lineage is

unknown.[40] If treatment is initiated at least 30 days before the onset of proestrus, estrus can be postponed for up to 2 years. Following cessation of the treatment, return to estrus will occur within 70 days on average (1–7 months).[38] Continuous treatment up to 5 years has been demonstrated without data on reversal rates to normal fertility following cessation of long-term treatment. The original manufacturer recommended to not treat continuously for more than 24 months. Testosterone (weekly intramuscular injections of testosterone propionate 110 mg or oral administration of 25–50 mg of methyltestosterone twice weekly) also suppresses estrus in bitches.[41]

The most common side effects reported with androgen use in bitches is clitoral hypertrophy and vaginitis.[39,42] Other side effects include increased body odor, urinary incontinence and spraying, mounting behavior, cervical dermis thickening, and epiphora.[11,38,42] It is important to note that androgens are contraindicated for use in Bedlington terriers because of an increased risk of hepatic dysfunction and in patients with androgen-responsive neoplasias.

Gonadotropin-Releasing Hormone Agonists

GnRH acts as the master reproductive hormone through regulation of the release of LH and FSH from the pituitary. In females, both LH and FSH are required to stimulate the ovarian changes leading to ovulation. However, sustained exposure to GnRH reduces GnRH-stimulated gonadotropin secretion through GnRH receptor downregulation, internalization, signal uncoupling, and a decrease of receptor expression.[43] Within the past 2 decades, long-acting GnRH agonists have been developed for canine estrus suppression.[44,45] GnRH agonists mimic GnRH by initially stimulating LH and FSH secretion (flare-up effect), which is generally regarded as an inherent disadvantage because it will induce estrus and delays the effects of estrus suppression by 7 to 14 days.[46] The induced estrus is associated with normal estrous signs (eg, vulvar edema, sanguineous vaginal discharge, estrous behavior).[47–49] The duration of the induced estrus is shorter compared with a natural estrus,[50] but the fertility in the induced estrus was high (ovulation rate, pregnancy rate, litter size) and not significantly different from untreated cycles.[50,51]

Biocompatible subcutaneous implants containing 4.7 mg or 9.4 mg of deslorelin acetate (Suprelorin) are commercially available in Europe, Australia, and New Zealand and labeled contraception of male dogs with a 98% efficacy for at least 6 months.[52] Although an extralabel application, when Suprelorin was administered to anestrous bitches, an ovulatory estrus was induced 4 to 8 days after implantation because of the initial flare-up effect, which was followed by estrus suppression up to 27 months.[53] When a subcutaneous deslorelin implant was administered to prepubertal female dogs, estrus was suppressed for 23 months.[54]

A subcutaneously administered goserelin acetate implant (Zoladex) containing 3.6 mg of goserelin suppressed estrous cyclicity for 12 months.[55] In addition, several buserelin acetate implants labeled for human reproductive purposes are commercially available (eg, Suprefact). Male dogs treated with a single buserelin implant containing 3.3 mg had testosterone suppression and suppression of spermatogenesis for 6 to 12 months. Recent data in female dogs show that buserelin implants will result in estrus suppression following an initial flare-up similar to what has been reported for deslorelin.[56]

The predominant complication of GnRH agonist administration for estrus suppression is the initial flare-up. When administered to some diestrous bitches (serum progesterone concentrations >5 ng/mL), the initial flare-up was suppressed.[53,57,58] However, several other investigators reported estrous signs after administering deslorelin implants to diestrous bitches.[47,59,60] Administration of MA concurrently

with a deslorelin implant has also been widely investigated. Treatment with MA (2 mg/kg) for 14 or 21 days beginning 1 week before deslorelin implant administration prevented the estrous response, but a lower dose (1 mg/kg) of MA would not.[57] Corrada and colleagues[61] (2006) reported that administration of MA (2.2 mg/kg) for 8 days with the deslorelin implant administered on the fourth day was more effective at preventing the initial flare-up than when deslorelin was administered on the first day.

Another limitation to this method of estrus suppression is that the duration efficacy seems to be dose related, and even at the same dose, varies greatly between individuals.[53] However, research in males has shown that multiple serial implant administration did not cause adverse effects or diminished efficacy. Dogs that have been reimplanted for 4 consecutive doses at 6-month intervals with the 4.7 mg deslorelin implant returned to normal steroidogenesis after cessation of treatment.[62] Serial studies similar to this have not been reported for females; however, females that have received implants have had normal fertility at subsequent estrous cycles.

Side effects reported following deslorelin implant administration include persistent estrus (including ovarian cysts, 15%), induced lactation (11%), some behavioral changes (6%) and miscellaneous problems (cystitis, vomiting, allergic reactions; 2%),[60] and pyometra (1 case reported).[63] For this reason, GnRH agonist implants should be subcutaneously administered cranial to the umbilicus in case removal becomes necessary.[64]

Gonadotropin-Releasing Hormone Antagonists

Both GnRH agonists and antagonists suppress gonadotropins and gonadal steroids, but administration of agonists is accompanied by an initial gonadotropin and gonadal hormone surge that will induce estrus in anestrous bitches. GnRH antagonists directly block pituitary GnRH receptors resulting in immediate suppression of gonadotropin release.[45,65] This suppression leads to an immediate dose-related arrest of gonadotropin secretion without the initial flare effect.[46,65] The degree and duration of LH and FSH suppression depends on the amount of GnRH antagonist administered.[66]

In general, GnRH antagonists require high doses to competitively inhibit responses to endogenous GnRH.[45] Subcutaneous administration of acycline (0.11–0.33 mg/kg) to bitches in early proestrus (<3 days) suppressed estrus for 3 weeks without any side effects observed.[67] If acyline is administered to anestrous bitches within the first 48 hours after administration of a long-acting deslorelin acetate implant, the initial ovarian stimulation and ovulation are not prevented,[68,69] suggesting that GnRH agonist stimulation overrode the effects of the GnRH antagonist.[70]

Other GnRH antagonists have been used in humans (degarelix for prostate cancer,[71,72] cetrorelix for infertility,[73] sufugolix for postmenopausal women,[74] relugolix for uterine fibroids,[75] elagolix for endometriosis).[76,77] However, a common problem with all GnRH antagonists is that they must be administered by injection.[78]

SUMMARY

In summary, surgical sterilization will likely remain the procedure of choice for permanent estrus suppression within the United States. However, practitioners have several options for short-term, reversible estrus suppression in dogs. Reproductive and nonreproductive side effects (eg, progestogens, androgens) and product availability (eg, mibolerone, deslorelin) continue to be significant limiting factors to greater adoption of these methods in veterinary practice. There is great hope for continued improvement in GnRH antagonists increasing their applicability for use in canine estrus suppression.

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