Review Article

Clinical Applications of GnRH Agonist Deslorelin in Dogs and Cats

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Abstract

The potent GnRH agonist deslorelin, formulated in a low dose, slow-release implant, is commercially available in many countries and its use is increasingly becoming more common in small animal reproduction practice. Although approved only for long-acting reversible contraception and in the control of androgen-related disorders in male dogs, deslorelin (Suprelorin®) has been used off-label in various aspects. The benefits in clinical practice are due to both the flare effect (immediate response) and down-regulation (chronic response) of GnRH receptors. Based on research and clinical data published recently, the clinical applications in dogs and cats include contraception, oestrous induction, management of benign prostatic hyperplasia, treatment of post-spays urinary incontinence and treatment of sex hormone-related behavioral problems.

Keywords: canine, Deslorelin, feline, GnRH analogue, reproduction,

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Introduction

A synthetic GnRH has been generated to modify the release of pituitary gonadotropins FSH and LH for therapeutic purposes by interacting with the GnRH receptor. Modifications of the decapeptide structure of GnRH provide two types of the analogue; GnRH antagonist and GnRH agonist. Administration of GnRH antagonist completely blocks and inhibits GnRH-induced receptor gene expression, leading to an immediate drop in FSH and LH secretion. In contrast, GnRH agonist activates the GnRH receptor causing hypersecretion of circulating FSH and LH that are accompanied by elevated concentrations of sex steroid hormones, so-called flare effect. Interestingly, after the initial stimulatory effect, multiple doses or continued low level dosing of GnRH agonist results in a down-regulation of its receptors on the pituitary gonadotropes and a shutdown of gonadotrophin FSH and LH release which subsequently suppress reproductive function in animals (Trigg et al., 2001). Down-regulation of receptors is believed to involve agonist-occupied receptors (Barden et al., 1989). Furthermore, chronic use of GnRH agonist causes desensitization of the Leydig cells to LH in the dog (Junaidi et al., 2007). At present, very potent agonistic analogues of GnRH in a slow-release formulation are commercially available in veterinary market and undergoing clinical evaluation in many species.

GnRH agonist deslorelin

Deslorelin, an injectable GnRH super-agonist, has been primarily approved for use in equine assisted reproduction (induction and timing of ovulation in oestrus mares) as a single subcutaneous short-term implant (Ovuplant®). In dog, the potent GnRH agonist deslorelin is formulated in a low dose, slow-release implant (Suprelorin®). It was registered for male dog contraception in Australia since 2002 and a year later in New Zealand. In the European Union (EU), the implant has been commercially available since 2008. In addition, deslorelin is recommended in the control of androgen-related disorders (e.g. benign prostatic hyperplasia) and unacceptable behavior because of its suppressive effect on pituitary-gonadal axis. The use of deslorelin is increasingly becoming more clinically relevant to small animal reproduction.

Use of deslorelin for contraception

In deslorelin-treated dogs, a rise in plasma LH levels is observed as early as 20 min after implantation and lasts for 80 min. Thereafter, LH levels decline to baseline after 3 days and become undetectable around 12 days after implantation. Similarly, despite a slight delay, duration of an acute increase in plasma testosterone is between 60 and 120 min, after which the level declines to a pre-treatment value on day 6 onwards and is undetectable after 12 days of implantation (Junaidi et al., 2009). As testosterone is prerequisite to maintain spermatogenesis, azoospermia is observed throughout the period that testosterone has been suppressed (Ponglowhapan et al., 2002[a]; Junaidi et al., 2009). Unlike the rat, canine is highly sensitive to the suppressive effects of GnRH agonists on testicular function, which appear to be mediated solely through pituitary down regulation (Vickery et al., 1983; 1984). Results from previous studies showed marked reduction in testicular volume and azoospermia in all deslorelin-treated dogs, and the period where ejaculates could no longer be obtained was dose-dependent varying from 5 to 10 weeks after implantation (Ponglowhapan et al., 2002[a]; Juanidi et al., 2003; 2009). At dose of 0.5-1 mg/kg body weight deslorelin, no ejaculates take place from approximately 6 weeks (range 4-16) following implantation and remains unobtainable for 28 weeks (range 22-38) (Ponglowhapan et al., 2002[b]). Although interval between implantation and the effect on contraception being effective seem variable from one individual to another, according to the manufacturer's recommendation, deslorelin-treated dogs are advised to be kept away from oestrous bitches for 4 weeks after implantation. Moreover, because treatment-induced effects are reversible, repeat treatment is scheduled every 6 months for implant containing 4.7 mg and every 12 months for 9.4 mg deslorelin.

In tomcat, a recent study by Goericke-Pesch et al. (2011) showed treatment with 4.7 mg deslorelin resulted in decreased plasma testosterone levels, decreased testicular volume and disappearance of the penile spine. Despite that semen parameters were not included in this study, an arrest of spermatogenesis (infertility) is expected following full down-regulation of testosterone. An additional period after complete ceasing of testosterone production (<0.1 ng/ml) until a deslorelin-treated tom become azoospermic is required for the purpose of contraception.

Although approved only for male dog, deslorelin has been used off-label in many bitches. Application of deslorelin implantation as a contraceptive in female dog and cat is still not clinically practical because of mainly its initial stimulatory effect that leads to the onset of oestrus. This is commonly seen in adult bitches in anoestrus (Trigg et al., 2001). A previous study showed that when deslorelin-induced oestrus bitches were bred, the pregnancies failed at about day 40 of gestation associated with low plasma LH concentrations and subsequent regression of corpus luteum (Wright et al., 2001). Similar results were observed in a study by Lueponglukana (2010) where loss of pregnancy was found around day 52 in deslorelin-treated bitches; interestingly, one bitch remained pregnant to term and whelped normally. Progesteronemia (dioestrus) has been demonstrated to prevent oestrus in implanted bitches (Trigg et al., 2001; Romagnoli et al., 2009); however, increasing evidence shows that some dioestrus bitches with high progesterone concentrations exhibit signs of oestrus even the plasma progesterone is greater than 60 ng/ml (Palm and Reichler, 2010; Fontaine and Fontbonne, 2010). Interestingly, oestrus induction in response to deslorelin is inhibited in progestin-treated bitches (Wright et al., 2001). Further investigation on a satisfactory protocol to inhibit the "flare effect" of

deslorelin implant in female dogs remains to be elucidated. In female cats, induced oestrus behavior is erratic although the initial fecal oestradiol concentration is detected in all implanted animals (Munson et al., 2001).

Recently, a retrospective study reported adverse effects of deslorelin in treated bitches that include mainly prolonged uterine bleeding (metropathy) especially in elderly dogs (Palm and Reichler, 2010). Additionally, follicular cysts, prolonged oestrus and pyometra have been reported in a 7-year-old bitch receiving 4.7 mg deslorelin to prevent oestrus (Arlt et al., 2011).

Use of deslorelin for oestrus induction and breeding

Studies showed that female dogs treated with deslorelin implants came into heat within 3-5 days post-implantation and ovulation occurred between day 11 and 15 of treatment (Kutzler et al., 2002; Fontaine and Fontbonne, 2010). To avoid pregnancy loss due to progesterone depletion caused by the constant use of deslorelin, removing the implant before ovulation (around the time of LH surge) (Kutzler et al., 2002) or after ovulation (Fontaine and Fontbonne, 2010) has been suggested. Anovulatory oestrus may occur if bitches are treated with deslorelin during early anoestrus or early removal of the implant before ovulation take place (Fontaine and Fontbonne, 2010). Although pregnancy rate up to 65% could be achieved from deslorelin-treated bitches, loss of litters prior to term (30 to 58 days of pregnancy) is frequent (Kutzler et al., 2002; Fontaine and Fontbonne, 2010).

Use of deslorelin in the treatment of benign prostatic hyperplasia (BPH) in dog

The size of the prostate is androgen-regulated. More than 80% of sexually intact male dogs (>5 years old) have gross or microscopic evidence of BPH (Atalan et al., 1999). Castration is traditionally recommended for BPH dogs. However, this option is not for stud dogs or aged dogs specifically those which have complicated health problems due to a high risk of anesthetic concern. Finasteride is a good alternative but daily drug administration to the animal may not be practical in certain circumstances. In this light, effective medical intervention that lowers testosterone levels is required.

The effect of deslorelin implant on prostatic volume in normal healthy entire dogs was studied by Ponglowhapan et al. (2002[b]). Chronic implants containing deslorelin (0.5-1 mg/kg) result in a significant reduction in prostatic volume from week 6 of treatment and the prostate returns to the pre-treatment volume by week 48 (Ponglowhapan et al., 2002[c]). Because the physiological response of normal and hyperplastic prostate may differ, evaluation of the efficacy of the implant in clinically ill dogs due to BPH has been conducted (Ponglowhapan and Lohachit, 2010). Recovery of clinical signs related to BPH is observed within the first 2 weeks of treatment, and deslorelin-induced prostatic regression as determined by measurement of prostatic dimension and volume ultrasonographycally was observed in all BPH dogs. Prostatic volume significantly decreases from day 16 to 210 of observation period. It is worth nothing that significant regression of the prostate induced by deslorelin is more rapid in BPH (day 16) compared to normal healthy dogs (week 6)(Ponglowhapan et al., 2002[c],Ponglowhapan and Lohachit, 2010). In line with our findings, successful treatment of dogs suffering from BPH have been demonstrated (Romagnoli, 2006; Jurczak et al., 2010; Ström et al., 2010), thus, indicating the efficacy of deslorelin in treating clinical BPH.

Use of deslorelin in the treatment of post-spay urinary incontinence in female dogs

Urinary incontinence affects up to 10-20% of spayed bitches but less than 1 % of intact bitches and is only sporadically reported in male dogs. Gonadectomy has an impact on hormonal homeostasis which contributes to a reduction in sex steroid hormones and a marked increase in the gonadotrophins LH and FSH in both male and female dogs (Reichler et al., 2004). A considerable increase in circulating LH and FSH raises the question whether these changes are responsible for the development of incontinence because this condition mainly affect spayed rather than intact bitches. Intriguingly, recent studies have shown that lowering plasma LH and FSH concentrations with GnRH agonist/antagonist implants, e.g. deslorelin, in 12/13 post-spay incontinent bitches that do not respond to classic medical treatments, i.e. oestrogen therapy or alpha-adrenergic receptor agonists, results in a temporary return continence or an improvement of the symptoms (Reichler et al., 2003; Reichler et al., 2006), implying that elevation of plasma gonadotrophin LH and FSH levels have a role in the pathophysiology of spay-induced incontinence in the dog. Differences in the expression of LH and FSH receptors in the canine lower urinary tract between intact and spayed bitches substantiate this notion (Ponglowhapan et al., 2008).

Use of deslorelin in the treatment of behavioral problems

In tomcat, sexual behavior like urine marking disappears within 11-16 weeks post-implantation (Goericke-Pesch et al., 2011). Data collected in Sweden (2006-2008) revealed the stated indications for use of deslorelin implants including the treatment of exaggerated sexual behavior and aggressiveness in male dogs (Ström et al., 2010). However, few dogs had increased sexual behavior or aggressiveness in the first month of treatment.

Side Effects of deslorelin implant

The adverse effects of deslorelin in treated bitches have been described recently (Palm and Reichler, 2010; Fontaine and Fontbonne, 2010). Prolonged bloody vaginal discharge or persistent heat especially in elderly dogs was mainly observed. Few individuals were affected by urinary incontinence and coat modification. Similarly, follicular cysts, prolonged oestrus and subsequent pyometra were reported in a 7-year-old bitch receiving 4.7 mg

deslorelin to prevent oestrus (Arlt et al., 2011). Little information is documented regarding the side effects in males.

Conclusion

Subcutaneous administration of the potent GnRH agonist deslorelin formulated in a low dose, slow-release implant is an effective reversible non-surgical castration of male dogs. In addition to the ability to inhibit testicular function, deslorelin has great potentials of therapeutic aspects to various disorders that related to the patho-physiological regulation of the hypothalamus-pituitary-gonadal axis. However, further investigation on its therapeutic efficacy and adverse effects remains to be elucidated as the actual mechanism of GnRH action, either directly or indirectly, on organs other than the reproductive system is not fully understood.

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