ABSTRACTS

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New indications of a GnRH agonist deslorelin in small animal reproduction: An update

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INTRODUCTION: Surgical contraception referring surgical removal of the gonads under general anaesthesia results in an irreversible and a permanent cessation of the reproductive function. However, because of the short and long-term complications of gonadectomy or the ethical reasons or the use of the animal, less invasive, reversible and safer techniques or therapies have been investigated for the control of reproduction in small animals. The advent of depot formulations that release gonadotropin-releasing hormone (GnRH) agonists such as deslorelin has drawn much more attention in the last decade. Today, deslorelin is commercially available as an implant in two dosage formulas (4.7 mg or 9.4 mg) in most European countries and licenced for the long-term control of fertility of adult male dogs.

Neurons in the hypothalamus produce gonadotropin releasing-hormone which stimulates secretion of the gonadotropins FSH and LH from the anterior pituitary gland. The release of FSH and LH results in production of testosterone in the male and oestrogen and progesterone in the female (Figure 1a). After subcutaneous implantation, deslorelin initially causes immediate release of FSH and LH from the anterior pituitary gland for several days due to the up-regulation mechanism and thus an increase in the concentrations of gonadal sex hormones (Figure. 1b). Constant release of deslorelin from the implant results in suppression of FSH and LH secretion because of the down-regulation of the GnRH receptors on the gonadotroph cells which in turn causes low levels of gonadal steroid hormones (Figure 1c).

Figure 1: A schematic diagram demonstrating the mechanism of deslorelin on the hypothalamic-pituitary-gonadal (HPG) axis in male and female animals. a. normal HPG axis; b. marked release of LH and FSH from the anterior pituitary gland resulting in increased gonadal steroid hormone levels following the deslorelin implantation due to up-regulation; c. marked decrease of LH and FSH release from the anterior pituitary gland resulting in decreased gonadal steroid hormone levels.

In this review, recent indications of deslorelin treatment have been discussed in details.

Previous indications of deslorelin:

Prevention of breeding in dogs and cats: Reversibility of fertility has been shown in different studies and estrus and pregnancies have been seen in bitches after chronic treatment with deslorelin. An estrus-like increase in E₂ concentrations are generally seen in treated queens but these E₂ peaks are not followed by behavioral estrus and mating. If queens mate at this time pregnancy should not be occurred with a 9.5 mg implant, because of the lower concentration of LH and progesterone.
No abnormalities in ovaries and uteri have been documented so far after treatment with deslorelin implant in queens. Body weights of queens may increase after application of implant when used for long-term contraception. Reversibility of fertility was shown after chronic treatment with the implant (1).

Induction of oestrus in female dogs: Immediate up-regulation and increased release of FSH and LH induces oestrus in bitches treated with deslorelin within 3-5 days following implantation. Pregnancy rates of up to 65% have been reported although loss of litters has been a frequent reported complication.

Treatment of testosterone dependent behavioral problems in male dogs: In a survey study (2), the owners stated that deslorelin has been used with some success in male dogs for the treatment of exaggerated sexual behavior (40%) and for aggressive behavior (16%) although in 8% of the cases an increased aggressive behavior one month after implantation have been noticed.

New indications of deslorelin

Treatment of canine benign prostatic hyperplasia (BPH): BPH is a spontaneous, age related and androgen-dependent prostatic disease of intact male dogs causing one or more of the following clinical signs: blood dripping from the tip of penis, haematuria, haemospermia, dysuria, infertility, feacal tenesmus and caudal abdominal pain. Cessation of testosterone production and thus disappearance of the clinical signs within two to four months without any additional pharmacological treatment has been demonstrated. Local or systemic side effects have not been observed in any of the dogs treated with deslorelin (3).

Treatment of urinary sphincter mechanism incompetence (USMI): Involuntary loss of urine or USMI occurring mostly during a sleep or recumbency is a long-term complication of gonadectomy in the female dog affecting up to 20 percent of the spayed dogs. Continence has been achieved in bitches with USMI following deslorelin that have not responded to medical therapies with oestrogens or α-adrenergic agonists (4). The success of deslorelin treatment in USMI patients was probably due to causative role of high FSH and LH levels in the development of USMI in spayed bitches.

Postponement of puberty in male and female cats: The efficacy of deslorelin for the postponement of puberty in cats has been recently investigated using 9 female and 3 male cats. Puberty could be postponed in all cats that have completed the study for 1-to-2 years by the use of deslorelin implant. Despite the absence of penile spines in deslorelin implanted cats throughout the study, testicular length, diameter and volume have increased significantly during the study period. Likewise, a significant increase in the body weight in all male and female cats has been found. In conclusion, the authors suggested that deslorelin could have been considered as a safe method to postpone puberty in the queen where as more data were required to draw the same conclusion in tomcats (5).

Control of fertility in the male ferrets and treatment of hyperoestrogenism in spayed ferrets (*Mustela putorius furo*): Surgical removal of the gonads in both genders of ferrets causes the development of hyperadrenocorticism, due to the post-operative lack of negative feed-back on the HPG axis. Deslorelin implant successfully suppressed plasma FSH and testosterone concentrations as well as spermatogenesis and reduced testis size (6).

CONCLUSION: Deslorelin implants can be used safely for various reproductive conditions as well as for effective non-surgical contraception in dogs and cats. Reversible inhibition of reproduction and long-acting feature of implant is potential benefits. Further investigations are needed to demonstrate the direct or indirect effects of GnRH action on non-reproductive organs and on ovarian interstitial tissue (1).

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(4) Reichler IM, Hubler M, Jöchle W, Trigg TE, Piche CA and Arnold S. Theriogenology 2003;60:1207-1216