Review Article

Clinical Use of Deslorelin (GnRH agonist) in Companion Animals: A Review

X Lucas
Department of Animal Medicine and Surgery, Veterinary Teaching Hospital, University of Murcia, Espinardo, Spain

Contents
Over the years, many contraceptive medications have been developed for companion animals, but many secondary adverse effects have limited their use. A major advancement was achieved with the use of gonadotropin-releasing hormone (GnRH) analogues, mainly GnRH agonists, which mimic the effects of native GnRH. The development of effective low-dose, slow-release implants with potent agonists such as deslorelin (Suprelorin®, Virbac) have allowed their use to become widespread in recent years, with many potential benefits in companion animals. While the major application of deslorelin was initially male contraception, due to its two differing actions, either the stimulation of oestrus or the sterilization of fertility, its use has been increasing in the bitch as well. The aim of this study is to review the applications of deslorelin GnRH agonist implants in companion animal, such as dogs, cats and some exotic pets.

Introduction
For many years, surgical castration has been the only reliable and permanent method of contraception in small animals. However, in many countries, discussion and even controversy surround the benefits and risks associated with these procedures (Reichler 2009). Over the years, many contraceptive medications have been developed. In approximately 1960, with the availability of orally active and increasingly more effective progestins in humans, efforts began to control reproduction in dogs and cats. Many types of progestins, oral or injectable, have been used for oestrous control in small animals. However, in all species, the secondary adverse effects of progesterone-type drugs limit their use and vary depending on when treatment is given in relationship to the stage of the oestrous cycle. An ideal non-surgical sterilant would be safe, effective, permanent, administered as a single injection and capable of being manufactured inexpensively (Struthers 2012). One approach in recent years has been the development of gonadotropin-releasing hormone (GnRH) analogues. GnRH is a decapeptide hypothalamic hormone that has the same amino acid sequence in all mammals. Modifications of the decapeptide structure of a GnRH agonist provide two types of analogues: GnRH antagonists and GnRH agonists. GnRH antagonists bind to the GnRH receptor (GnRHRr) and completely block LH/FSH secretion and the activation of downstream signalling pathways that stimulate gonadotropin biosynthesis. Once GnRH agonist administration is discontinued, the animal becomes fertile, but the timeframe is unpredictable.

Since 1971, many GnRH agonists have been developed for use in human medicine, with multiple applications in reproduction, oncology and other fields. Initially, the main disadvantage of the use of agonists was the need for frequent subcutaneous (SC) injections or SC mini-pumps over prolonged time periods to mimic the natural secretion of GnRH. Another impediment to progress with GnRH agonists has been the cost of production and the lack of a cost-effective means for delivering adequate doses over a prolonged period (Junaidi et al. 2003). In recent years, effective low-dose, slow-release implants containing potent agonists (superagonists) have been commercialized for use in veterinary medicine in the European Union (EU), such as deslorelin and azagly-nafarelin (Herbert and Trigg 2005; Gobello 2007). In companion animals, the deslorelin implant (Suprelorin® Virbac, Carros, France) is the most commonly used in small animals. Compared to natural GnRH, deslorelin has chemical modifications in its amino acid composition at positions 6 and 9/10. This compound was registered for male dog contraception for the first time in Australia in 2002 and has not been available in the EU since 2008. In contrast to humans, no side effects have yet been reported in treated animals. GnRH agonists/antagonists may either stimulate oestrous or effectively sterilize the patient, depending on the duration of action and the dosage applied. The aim of this study was to review the applications and treatments of the deslorelin (GnRH agonist) currently used in companion animal medicine.

Deslorelin Use in Male Dogs
Many studies have probed the use of GnRH agonists for chemical reversible sterilization in males (Fontaine and Fontbonne 2011). The first report of chemical sterilization in a dog was published in 1984 (Vickery et al. 1984). This effect is the main reason for the clinical use of GnRH agonists in companion animals. As described above, after the ‘flare-up’ effect, the second action of a GnRH agonist is related to the desensitization of the GnRHR to GnRH, which results in a temporary long-term, fully reversible downregulation of testicular endocrine function in male dogs (Trigg et al. 2001; Junaidi et al. 2003). With regard to deslorelin, the first study was performed in 2001 (Trigg et al. 2001) using a 6-mg implant. Thereafter, several studies were performed (Ponglowhapan 2002; Ponglowhapan et al. 2002; Junaidi et al. 2003, 2007, 2009; Romagnoli et al. 2005, 2012; Trigg et al. 2006; Ponglowhapan and Lohachit 2010) using different concentrations of deslorelin (2.1, 4.7, 6, 9.4 and 12 mg/implant). These studies reported deslorelin implants as a safe and well-tolerated sterilization method. Furthermore, repeated implantation following
recovery from an initial implant indicated that the effect of deslorelin could be reinstated in previously treated dogs and prolonged. Moreover, regardless of the deslorelin implant concentration, following the loss of efficacy of these implants, all treated dogs reached physiological testosterone levels within 7–9 weeks, and seminal quality recovered fully.

In general, an increase in plasma levels is observed as early as 20 min after deslorelin implantation (Junaidi et al. 2007). These levels decline to basal values after 3 days and are not detectable approximately 12 days after implantation. Similar results have been observed regarding the plasma testosterone concentrations. Initially, 60–120 min after deslorelin implantation, there is an acute increase in testosterone values, but it is undetectable in the majority of dogs 12–17 days after implantation (range 6–25 days) (Trigg and Yeates 2008; Junaidi et al. 2009). Regardless of size, all the dogs treated with a 4.7-mg deslorelin implant exhibit testosterone levels of <0.4 ng/ml from 22–33 days to at least 180 days (Trigg et al. 2006). The decreased levels of gonadotropins and plasma testosterone concentrations explain the marked reduction in testicular volume and azoospermia in deslorelin-treated dogs. Importantly, however, the response was very variable from one individual to another (Fontaine and Fontbonne 2011), and the duration of inhibition of testosterone secretion/spermatozoa depends on the concentration of the deslorelin implant and the size of the dog. The dose–response relationship is not expressed in the degree of suppression of reproductive function but in the duration of suppression, with a 6-mg or 9.4-mg slow-release implant reducing the production of testosterone and spermatozoa for up to one year (Trigg et al. 2001; Junaidi et al. 2003). However, with a 4.7-mg implant, the blood testosterone concentration remains low for an average of 400 days in dogs weighing more than 25 kg. It has proven impossible to suppress testosterone for more than 400 days (Trigg et al. 2006). Implants with 9.4-mg deslorelin were effective in reducing testosterone to <1 ng/ml for periods of up to 400 days (Trigg et al. 2006). In one study, dogs treated with 12-mg implants took the longest time until full restoration of ejaculates (Junaidi et al. 2009). The decrease in testosterone levels is typically accompanied by a decrease in testicular volume. Indeed, in the same study, the testicles reached a minimum volume of approximately 35% of the initial volume 4–5 weeks after implantation in all implanted dogs (Junaidi et al. 2009).

In regard to azoospermia, Junaidi et al. (2007) concluded that changes in testosterone concentration reflect passive responses to changes in LH secretion by desensitization of the GnRHr; however, they can also be caused by changes in the responsiveness or desensitization of Leydig cells to LH by approximately 4 weeks after implantation. These hormonal changes explain the progressive decrease in ejaculate volume, sperm concentration and sperm motility that lead to complete infertility 6 weeks after implantation (Junaidi et al. 2003). Trigg et al. (2006) reported that the percentage of abnormal forms increased more than 10-fold in the 35 days following the insertion of a 4.7-mg deslorelin implant. In agreement with Junaidi et al. (2009), a study performed by Polisca et al. (2013) reported a decrease in semen quality observed days 22–37, when it was no longer possible to obtain ejaculate. Furthermore, using electron microscopy, another study demonstrated in dogs treated with deslorelin for 41 and 101 days that the Sertoli cells were smaller, the nucleoli of the Leydig cells were atrophied, and the prostate glandular epithelium showed reduced epithelial height and atrophy (Junaidi et al. 2009). From a practical point of view, deslorelin implant manufacturers recommend that treated dogs are kept away from bitches in oestrus for 4 weeks after implantation (Ponglowhapan 2011).

Complete recovery of seminal quality has been achieved for all dogs at all tested doses, but is quite variable. The time for recovery of steroidogenesis has been reported to be variable, with smaller dogs (<10 kg) in general taking longer to recover than medium or large dogs (Trigg et al. 2006). It is recognized that the normal spermatogenic cycle is approximately 9 weeks. The return to full sexual competence in terms of viable semen counts, volume (prostatic function) and mating behaviour (ejaculation) will take a further 2–3 weeks. It is expected that dogs will remain sexually incompetent for up to an additional 9 weeks after deslorelin cessation (Trigg et al. 2006).

Recently, Romagnoli et al. (2012) detailed changes in canine semen quality after the administration of 4.7-mg deslorelin implants. The authors concluded that the semen quality may not be negatively affected initially and that some seminal parameters, such as spermatozoa motility or concentration, can be improved during the first month after implantation. Using frequent injections of other GnRH agonists, such as buserelin, a transient improvement in spermatogenesis in canine testes has been reported (Kawakami et al. 2012). The results of Romagnoli et al. (2012) open the possibility of temporarily using this implant (with its removal) in cases of subfertile dogs to improve semen quality.

Note that in addition to contraception, GnRH agonists also cause significant shrinkage of the prostate gland (Junaidi et al. 2009; Polisca et al. 2013), which is a clinical advantage for dogs with benign prostatic hyperplasia (BPH), a common condition in intact male dogs. The effects of deslorelin on prostate volume in healthy and clinically ill dogs with BPH have been evaluated by several authors (Ponglowhapan et al. 2002; Jurczak et al. 2010; Ponglowhapan and Lohachit 2010; Ström et al. 2010). These studies have shown a significant progressive reduction in prostate volume, more rapid in BPH compared to normal healthy dogs with a resolution of clinical signs within the first 2 weeks of treatment (Ponglowhapan and Lohachit 2010). Recently, Polisca et al. (2013) reported a more marked reduction in prostate volume in a shorter period compared with the previous studies (starting at day 37 after implantation) with the use of a 4.7-mg deslorelin implant in dogs with BPH. However, it is important to remember that initially, due to the ‘flare-up’ effect of deslorelin agonists, it is possible to increase the clinical signs associated with BPH. The ideal patient for this treatment is therefore considered to be the asymptomatic dog with BPH, to
prevent the progression of this prostate disorder (Polisca et al. 2013).

Another indication for the use of deslorelin in male dogs is to control certain objectionable behaviours linked to the action of testosterone. Some studies have revealed that surgical and chemical castration with 4.7-mg deslorelin implants induces similar effects with regard to decreased testosterone values and behavioural parameters, such as aggression (Ström et al. 2010), fear/insecurity, play and sexual behaviour in dogs (De Gier and Vinke 2010; De Gier et al. 2012). From the clinical point of view, the implants can be used to reliably produce the behavioural changes that result from surgical castration. Importantly, however, the perceived effect on sexual behaviour towards oestrus bitches is greater following surgical castration compared with the deslorelin implant, despite similar low basal plasma testosterone concentrations in both groups (De Gier et al. 2012).

To control unwanted births in dog populations, 4.7- or 9.4-mg deslorelin implants have been used to delay the onset of puberty in 4-months-old male pups (Sirivaidyapong et al. 2012). The higher concentration had a longer duration of action (>2 years, 30–36 months), whereas 4.7 mg was effective in delaying the onset of puberty for <2 years. No differences in growth, size, height, conformation or non-sexual behaviour between implanted dogs and control dogs have been reported (Sirivaidyapong et al. 2012).

Deslorelin in Tomcats

In feline reproductive medicine, GnRH agonists are gaining increased importance. The first study on the chemical sterilization of tomcats with the use of deslorelin (4.7-mg implant) was performed by Goericke-Pesch et al. (2010). Similar to dogs, the chemical sterilization effect seemed to be a decrease in testosterone levels after the initial flare-up effect; however, in cats, the initial testosterone increase was not significant, in contrast to the findings in dogs (Goericke-Pesch et al. 2011). Researchers found that testosterone levels declined rapidly on day 20 after implantation (<0.1 ng/ml) and were at basal concentrations for 11 weeks in the majority of the tomcats treated (Goericke-Pesch et al. 2011). However, a high individual variability has been observed in the response to treatment. The duration of efficacy varies between 6 and 24 months, with a minimum of 390 days of inhibition (4.7-mg implant) (Goericke-Pesch et al. 2010). Similar to dogs, it is possible to use repeated implantation. The main markers of cessation of testosterone production are testis volume reduction and the disappearance of penile spines. One study reported that the mean testicular size had decreased by more than 50% by week 12 and that this decrease was maintained as long as fertility was suppressed. The maximum reduction was 73.5% in week 36 (Goericke-Pesch et al. 2011). Additionally, the same authors reported that the penile spines disappeared in all the implanted toms after a mean of 9 weeks. Other side effects, such as a decline in body weight, decreased food intake and behavioural changes, have also been reported (Goericke-Pesch et al. 2010; Goericke-Pesch 2011). Between weeks 11 and 16 after treatment, the toms showed complete loss of sexual behaviour including urine marking; however, clinical observations demonstrated that even implanted males could mount and mate queens in oestrus (Goericke-Pesch et al. 2011).

As mentioned above, the main effect in the tomcat is the negative influence on male behaviour and changes in testicular size. However, there is limited information about the effect of deslorelin on semen quality and the return of sperm production in this species. Novotny et al. (2012) found histological changes (atrophy) in the seminiferous epithelium, but in contrast to dogs, the Leydig cells were easily identifiable 90 days after the placement of a 4.7-mg deslorelin implant (Ackermann et al. 2012a). A progressive decrease in seminal quality 2–3 months after implantation has also been observed (Novotny et al. 2012); however, one study has reported a highly individual response in regard to sperm concentration, suggesting that sperm production is only partly suppressed (Ackermann et al. 2012b). Histological studies have confirmed a rapid re-establishment of spermatogenesis 1 month after implant removal (Novotny et al. 2012), but more studies about the return of sexual activity are necessary. Finally, no studies on the use of 9.4-mg implants or the treatment of pathological conditions with the use of deslorelin have been reported in tomcats.

Deslorelin Use in Bitches

Although in the EU, deslorelin implants are only approved for male dogs, many studies have been performed in the bitch as to investigate its use as a contraceptive and/or method of oestrus induction (Table 1). As mentioned above, the first step in the mechanism of action is a flare-up effect with an increase in the synthesis of gonadotropins. This stimulating effect is more pronounced in females than in males. Thus, oestrus induction can be observed in the majority of bitches implanted in anoestrus, regardless of the stage of anoestrus (Volkmann et al. 2006a; Fontaine and Fontbonne 2010). The majority of authors have confirmed that all adult bitches respond the same way regardless of size and age; however, depending on the stage of the cycle, the response of the bitch can differ (Fontaine and Fontbonne 2011). Deslorelin implants can be used as an alternative to dopamine agonists to induce fertile oestrus in the bitch in anoestrus (Fontaine et al. 2011a). In general, the time of the appearance of serosanguinous vulvar discharge was similar using 4.7-mg deslorelin implants, ranging between 4 and 6 days after implantation (Fontaine et al. 2011a; Walter et al. 2011). Using 2.1-mg implants, proestrus signs began 6 days after implantation (Kutzler et al. 2002, 2009; Volkmann et al. 2006b). Ovulation occurred on average at 11 days post-implantation (range 8–16 days). There are differences among studies related to ovulation rate, time to implant removal and the pregnancy rates of the induced oestrus (Maenhoudt et al. 2012).

Regarding the percentage of bitches that ovulate, the stage of the oestrous cycle at the time of implantation (dioestrus, early anoestrus or late anoestrus) has been
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shown to influence the results. Although better ovulation rates were obtained in bitches implanted with 4.7-mg deslorelin during anoestrus, some studies have reported the highest percentage in late anoestrus (87.5%) compared with early anoestrus (62.5%) (Fontaine et al. 2011a). Volkmann et al. (2006b) induced fertile oestrus in bitches in dioestrus by inducing luteolysis with progestagens and then using 2.1-mg deslorelin implants, although only four of ten bitches ovulated and only one became pregnant. Additionally, in some bitches, anovulatory cycles induced with deslorelin implants have been reported (18.7%), although the cause of this remains unclear and requires further investigation (Volkmann et al. 2006a; Fontaine et al. 2011a; von Heimendahl and Miller 2012). The same authors recommend removing the implant 15 days after implantation if no ovulation has occurred. Some studies suggest the removal of the deslorelin implant when it is used for oestrus induction to avoid premature downregulation of the pituitary and possible hypoluteotroism. However, some authors reported that some bitches carried their pregnancies to term without the implant being removed, which suggests that downregulation may not be strong enough to induce luteal failure in all bitches (Volkmann et al. 2006b; Kutzler et al. 2009). Moreover, luteal failure was suspected in some bitches even after implant removal (Fontaine et al. 2011a). To avoid this phenomenon, instead of the normal site between the shoulder blades, implants were placed SC in an area where they could be easily removed, such as the post-umbilical area or the medial side of the leg.

In regard to the time of implant removal, initial studies recommended it at the beginning of prooestrus or at the time of the LH surge (Kutzler et al. 2002; Kutzler 2005). However, in more recent reports, the implant has been removed preferably at the time of ovulation (Fontaine et al. 2011a; von Heimendahl and Miller 2012; Wolf et al. 2012) because removal at this time has been shown to not significantly affect fertility parameters or to decrease the chances of an anovulatory cycles (Fontaine et al. 2011a).

Pregnancy rates following deslorelin implantation have varied between studies, but a rate of up to 65% could be achieved. von Heimendahl and Miller (2012) reported an 84.6% pregnancy rate in the bitches that are ovulated using 4.7-mg implants that were removed after ovulation, confirming the clinical data previously presented by Fontaine et al. (2011a). In both studies, the litter size obtained was considered normal in the breeds used. However, other authors in the same year, using a 2.1-mg deslorelin implant and the same bitches, observed that the mean litter size was lower with induced oestrus compared with natural oestrus (Wolf et al. 2012). Only a few side effects in a few bitches have been reported, such as persistent oestrus (Fontaine and Fontbonne 2011).

As mentioned above, the main problem with using deslorelin implants as a contraceptive method is the induction of oestrus in the majority of bitches implanted in anoestrus. The stage of the cycle at which the treatment is started appears to have no impact on the duration of oestrus suppression after implantation (Trigg et al. 2001) but is dependent on the deslorelin concentration (Sung et al. 2006). Similar to male dogs, there is high individual variability. With 2.1 mg deslorelin implants, oestrus can be suppressed for up to 27 months (Wright et al. 2001), but recent studies have suggested an average of 10.2 ± 5.1 months (2.1–23.3 months) with the use of 4.7-mg implants (Maenhoudt et al. 2012). Normal return to fertility after implantation has been suggested, but few clinical data are available.

The main studies that have been performed to prevent induced oestrus as a contraceptive effect of deslorelin implants are summarized in Table 1. Progestins have been the most used compounds because the first studies suggested that high plasma progesterone concentrations (up to 5 ng/ml) inhibited the induction of oestrus with the deslorelin implant (Trigg et al. 2001; Romagnoli et al. 2009). However, another report differed and showed oestrus signs in bitches implanted in dioestrus (Fontaine and Fontbonne 2011). Moreover, a great variability between bitches and between studies in regard to the prevention of oestrus induction has been observed. For this reason, deslorelin implants cannot be considered valuable alternatives to induced contraception in bitches. Side effects have been reported in a few bitches and include uterine diseases, urinary incontinence and coat modification (Palm and Reichler 2010).

Very few studies have described the delay of puberty using deslorelin implants in bitches, but in all of them, the results have confirmed them as an effective pharmacological contraception method. The age at implantation seems to play an important role in the response to

<table>
<thead>
<tr>
<th>Component</th>
<th>Treatment/number of females used (n)</th>
<th>Effect (% of bitches with no induction of oestrus)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progestins</td>
<td>Megestrol acetate (2 mg/kg/day for 14 or 21 days) starting 1 week or 2 weeks before a 6-mg implant/(n: 15)</td>
<td>100%</td>
<td>Wright et al. 2001;</td>
</tr>
<tr>
<td>Megestrol acetate (2 mg/kg/day/8 days) starting 4 days before a 10-mg implant/(n: 8)</td>
<td>50%</td>
<td>Corrada et al. 2006;</td>
<td></td>
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<tr>
<td>Oestrone acetate (0.5 mg/kg/2 days) on the second day, a 4.7-mg implant was inserted/(n: 16)</td>
<td>75%</td>
<td>Anjolras 2011;</td>
<td></td>
</tr>
<tr>
<td>GnRH antagonist</td>
<td>Acyclina (330 µg/kg) within the first 48 h after a 10-mg implant/(n: 12)</td>
<td>25%</td>
<td>Valiente et al. 2009;</td>
</tr>
<tr>
<td>Aromatase inhibitor</td>
<td>Anastrozole (0.1 mg/kg/15 days) at the same time as a 4.7-mg implant/(n: 3)</td>
<td>33.3%</td>
<td>Fontaine et al. 2011b;</td>
</tr>
<tr>
<td>Anti-oestrogen</td>
<td>Clomiphene acetate (5 mg/kg/15 days) at the same time as a 4.7-mg implant (n: 8)</td>
<td>37.5%</td>
<td>Fontaine et al. 2011b;</td>
</tr>
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the implants. In bitches aged 7 months or older, the 4.7 mg implant has been shown to induce oestrus in all dogs within 1-2 weeks; however, pups aged 4 months show no sign of oestrus for 36 weeks (Trigg et al. 2006). Maenhoudt et al. (2012), using 4.7-mg and 9.4-mg implants in bitches younger than 6 months of age of different breeds, observed no induced oestrus in any bitch or clinical side effects. The average delay of puberty was 13-24 months with implants of 4.7 mg. Marino et al. (2014), using the same implant in 4.5-month-old female dogs, postponed puberty at least 4.5 months, and the effect could be maintained with repeated treatments until 18 months. Interestingly, these authors reported that all the bitches showed a modest increase in the plasma levels of oestradiol and an evident cornification of the vaginal cells, but no external signs of oestrus or ovulation were detected. No histological changes were detected in the ovaries or uterus after ovariohysterectomy of the bitches at 18 months after the first implantation, but persistence of infantilism of the external genitalia was reported (Marino et al. 2014).

The use of deslorelin implants in the treatment of post-spaying urinary incontinence and spay-induced coat changes in female dogs has been reported. It has been suggested that, among other causes, increased levels of FSH/LH in spayed bitches are responsible for this type of incontinence and changes in coat. However, to the knowledge of the author, only two studies have been published with the use of 4.7- and 9.4-mg deslorelin implants (Reichler et al. 2008; Reichler 2010) in these clinical situations.

Deslorelin Use in Queens

In contrast to female dogs, in the queen, the main indication for the use of deslorelin is oestrus inhibition. The first report was published by Munson et al. (2001) with the use of 6 mg of deslorelin in 20 queens. This study confirmed that this agonist can be used to effectively suppress ovarian activity, but the duration of inhibition was highly variable among the individual queens (mean of 14 months). This variability has been reported by other studies, ranging from 6 to 37 months. However, reported by other studies, ranging from 6 to 37 months. However, this does not necessarily mean that deslorelin is contraindicated in queens; in fact, it has been suggested that deslorelin may be a useful tool in the management of oestrus inhibition in queens.

The reversibility of deslorelin treatment in female cats has been reported (Toydemir et al. 2012); however, only two reports have provided data about further fertility after the loss of deslorelin efficacy in queens. In 2012, Ackermann et al. reported the recovery of viable oocytes by surgery after short-term contraceptive treatment with 4.7-mg deslorelin implants (90 days of treatment followed by implant removal and hormonal ovulation induction 10 days later). Recently, a promising study by Goericke-Pesch et al. (2013) reported for the first time the return to fertility in all mated queens after the end of efficacy of 4.7-mg deslorelin implants, which was observed after naturally occurring oestrus, and no differences in fertility or litter size were reported compared with the control.

Similar to canine pups, deslorelin implants may also be used to postpone puberty in queens. Because domestic cats normally achieve puberty at approximately 75% of their adult body weight (Johnston et al. 2001), in this case, the implants (4.7-mg deslorelin) were administered to queens at 50% of their adult body weight (Risso et al. 2012). The results showed a significant delay in the onset of puberty in deslorelin-implanted queens (281.2 ± 21.6 days) compared with the control group (177.8 ± 10.8 days). Similar to dogs, growth was not altered by the implant, and no flare-up effect post-implantation was observed. However, a high variability in the effect duration was observed among treated queens (Risso et al. 2012).

Finally, a case report has recently described the use of deslorelin implant for post-spaying urinary incontinence in queens (Pisu and Veronesi 2014). The authors reported the treatment (4.7-mg deslorelin implant) of a 2-year-old female ovariectomized Norwegian Forest cat with a history of post-spaying urinary incontinence. The queen showed restored urinary continence approximately 25 days after implantation and maintained it for at least 15 months. However, to the knowledge of the author, no data about GnRHr expression in the urinary tract of the cat are available; therefore, additional investigations with a larger number of animals are needed.

Other Companion Species

The use and removal of deslorelin implants in other pets has been reported in the last few years. In ferrets, surgical contraception is related to hyperadrenocorticism, a common disease in castrated males and females (Schoemaker et al. 2000). Alternatively, the use of 4.7-mg and 9.4-mg deslorelin implants in males (Schoemaker et al. 2005; Vinke et al. 2008) and females (Prohazic et al. 2010; Goericke-Pesch and Wehrand 2012) is a promising and suitable method for contraception in this species and for treatment of the adrenal disease. Using 3-mg implants in ferrets with adrenal disease, one study reported that the clinical signs (vulvar swelling, pruritus, sexual behaviour and aggression) were significantly reduced or suppressed after 14 days of implantation. The mean time to recurrence of the signs was 13.7 ± 3.5 months (range 8.5–20.5 months) (Wagner et al. 2005). The efficacy of deslorelin as contraception ranged to more than 173 days in males, 122 days in...
females in anoestrus and more than 32 months in female ferrets (Schoemarker et al. 2008; Prohazic et al. 2012). Fertility after 4.7-mg deslorelin implantation also returned to normal, but only at the second post-treatment oestrus (Prohazic et al. 2012).

Recently, the use of deslorelin implants has been reported in pet birds (Mans and Pliny 2014). Deslorelin in avian species could also be useful for the treatment of diseases and unwanted associated reproductive behaviour, such as aggression, feather-destructive behaviour and/or masturbation (Petritz et al. 2013). Deslorelin (4.7 mg) has been used to decrease mean egg production, and its effect has been reported to begin at 2 weeks after implantation and last up to 12 weeks after implantation (Petritz et al. 2013). The minor duration in comparison with other species could be due to the inherent difference in drug metabolism in avian species and requires further investigation.

Finally, a short communication regarding the successful use of a 4.7-mg deslorelin implant to control increased aggression in a male pet bearded dragon has been published (Rowland 2011).

Conclusions

Since the first report of chemical sterilization in a dog in 1984, many studies have been published regarding the successful use of the GnRH agonist deslorelin in chemical reversible sterilization in male dogs. Similar to in dogs, the deslorelin implant can be used successfully as contraception in male cats. In contrast to dogs, the testosterone increase is not significant in cats, and much less data have been published about the return to fertility. In both species, a decrease in behaviour linked to the action of testosterone has been reported. Therefore, deslorelin implants can be used to predict behavioural changes resulting from surgical castration.

As mentioned in the review, the first step in the mode of action of a GnRH agonist is the ‘flare-up’ effect, with an increase in the synthesis of gonadotropins. This effect has allowed the use of deslorelin as a pro-fertility agent in female dogs. Deslorelin implants can be used as an alternative to dopamine agonists to induce fertile oestrus in bitches. However, in some bitches, anovulatory cycles have been reported, with possible luteal failure suspected. Therefore, some aspects, such as whether to remove the implant after the induction of oestrus and the bitch’s fertility and litter size after treatment, need to be clarified and standardized. In regard to the use of the deslorelin implant as an oestrus inhibition method in bitches, the initial ‘flare-up’ effect must to be avoided. The results obtained with different compounds, such as GnRH antagonists or progestins, are unclear and need further investigation. In the queen, the stimulatory effect is poorly described, and a high percentage of queens do not show oestrus signs. For this reason, the deslorelin implant can be used successfully in the queen for oestrus inhibition. However, more studies are needed to determine the reversibility and return to normal fertility after the loss of deslorelin efficacy in the queen.

Few reports have been published about the use of deslorelin implants to delay puberty in male and female dogs and in the queen. All of the examined studies have shown that puberty can be postponed for several months compared with control animals that are not implanted, and no influence on final size or growth has been reported. Finally, other research and published clinical data indicate that deslorelin can be used in disease conditions related to sex hormones, such as prostate diseases, post-spaying incontinence or coat-changes after spaying, and even in other clinical situations for ferrets or pet birds. However, few reports are currently available and further investigations of its therapeutic efficacy and adverse effects are necessary.

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Conflict of interest

The author has no conflict of interest to declare.

Author contributions

Prof X Lucas design and wrote the paper.

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Author’s address (for correspondence): X Lucas, Department of Animal Medicine and Surgery, Veterinary Hospital Teaching, University of Murcia, 30100 Espinardo, Murcia, Spain.
E-mail: xiolucas@um.es