Dear Colleagues,

We are very happy and proud to have the responsibility of writing this foreword for the abstract book of the Suprelorin® Symposium organised within the EVSSAR bi-annual congress of Louvain La Neuve.

The introduction to the European market of subcutaneous implants containing the GnRH agonist deslorelin (Suprelorin®) may well be considered as a revolution in the small animal reproduction world. In the past, previous products, such as cabergoline or aglepristone, proved to be in a way "revolutionary" molecules, bringing new knowledge and helpful procedures to small animal theriogenologists for research and clinical work. Suprelorin®, initially marketed for use in chemical prevention of reproduction in male dogs, is now also beginning to be used in numerous other indications. It is used in both males and females, dogs, cats, ferrets and other new companion animals, as such proving its high interest in the field of small animal reproduction but also stimulating new clinical approaches. This is indeed not surprising when one considers that hypothalamic GnRH plays a central role in animal reproduction, whatever the species.

For the past two years, many researchers and clinicians in Europe have begun trying to study eventual new indications of Suprelorin®, thus showing the enthusiasm of European small animal theriogenologists towards this new product. Of course, it is far too early to have a complete understanding of the clinical uses of Suprelorin®, but the aim of this Virbac-Suprelorin® symposium is to bring you an overview of what is going on at the moment, and which preliminary results have been obtained so far, in different species and for different indications. The goal is to look at available protocols for the use of Suprelorin® and give to specialists and practitioners alike recommendations to permit a more enlightened use of this compound. We hope that the veterinary profession as a whole will benefit from a clear position from experts that have already experimented in clearly and strictly defined conditions.

Wishing you a fruitful symposium.

Best regards.

Alain Fontbonne, DVM, PhD, Dipl. ECAR, EVSSAR Past-President
Maxime Albouy, DVM
Recent discovery on the mode of action of GnRH Agonists

I. GnRH controls pituitary gonadotropin secretion

Gonadotrophin releasing hormone (GnRH) is the master hormone controlling mammalian physiology. This neuropeptidal hormone is homogeneous across all mammals. GnRH is released by the hypothalamus level towards the pituitary gland. This pulsatile release stimulates secretion of the gonadotropins hormones LH and FSH.

In male dogs, Luteinising hormone (LH) binds to receptors on Leydig cells in the testis stimulating the synthesis and secretion of Testosterone. Follicle stimulating hormone FSH promotes spermatogenesis. The systemic release of Testosterone is responsible for a negative control on GnRH, FSH and LH release.

Hormones regulating the reproductive function are hydrosolubles peptides that cannot cross the lipid slay (hydrophobic) of the cellular membrane. Their action on target cells is mediated via external receptors on the membrane. Binding of the hormone to this receptor is specific and based on a physical complementary between the shape of the hormone and the receptors similar to the clé-serrue system.

E = Effector
D = Dynamine
P = Phosphore
S = GnRH agonist

2. Down-regulation/desentisation of GnRH-Recepter: the old conception

GnRH receptors (GnRH-R) belong to the family of receptors associated with G protein (GPCRs). The structure of these proteins contain 7 trans-membranaires domains linked with intra and extra cellular loops.

The mode of action of GPCRs involves phosphorylation and endocytosis mechanisms. Binding of GnRH agonists to the receptor synthesis of GTP resulting in the dissociation of the sub-units $\alpha$ and $\beta\gamma$ of the $G$ protein. The $\alpha$ sub-unit binds to the effector and induces transmission of the hormonal message. The GTPase of the $\alpha$ sub-unit recombine with the $\beta\gamma$ sub-unit releasing a phosphate that will phosphorylate the receptor. This new phosphorylation permit the binding with the $\beta$-arrestine. The $\beta$-arrestine generates the internalisation of the desensitised receptor (endocytosis pathway).

The action of the dynamine (GTPase) induces the split of the endosome and the plasmatic membrane. The receptor is then de-phosphorylated (= resensitisation) by a phosphatase (this process is facilitated by the acidification of the vesicular lumen). The receptor is degradayed by the lysosomes or recycled on the cellular surface (this explain the reproductive cycles).

3. GnRH regulates expression of gonadotropins subunit genes

In the past few years, two types of GnRH receptors have been identified: GnRH-R I and II. GnRH type I is the only one that plays a key role in the regulation of the reproductive function in mammals (type II would be involved in the regulation of hunger). There is no queue C terminale in the type I receptor sequence. However this termination is compulsory for the process of phosphorylation and binding to the $\beta$-arrestine.

Another mechanism is suspected for the response to the GnRH. This mecanim involves second messengers. The effector is a phospholipase C ; Its activation results in the hydrolyse of the phosphatidylinositol biphosphate (PIP2) into inositol triphosphate (IP3) and diacylglycerol.
IP3 induces an increase in Ca++ concentration into the cytoplasm. (opening of the calcium channel). The increase in Ca++ activates the protein-kinases Ca++-calmoduline dépendantes and the activation of a protéine kinase C (with the diacylglycérol). GnRH can also induce activation of phospholipases A2 et D and rise of intracellular levels in AMPc and GMPc.

The activation of these different pathways modulates the expression of the genes responsible for the gonadotropins sub-units expression,

4. Deslorelin is a GnRHa superagonist.

In the Deslorelin sequence, changes are made to endogenous GnRH at position six and nine in the amino acid sequence (Figure 1). The new entity is less susceptible to cleavage and therefore potency is improved, GnRH receptor binding affinity is much higher than that of endogenous GnRH (7 times higher).

References:

Clinical Use of Suprelorin® to control fertility in male dogs

Pharmacology
Suprelorin® is an implant that releases the synthetic GnRH agonist Deslorelin over many months. This constant release of high affinity GnRH causes a down regulation of the receptors in the pituitary and, after a short initial rise, a decrease in LH and FSH production. The lack of FSH and LH prevents testosterone production and spermatogenesis. This in turn causes a reversible, non surgical castration of the implanted male.

Use
One implant (Deslorelin acetate 4.7 mg) is placed subcutaneously between the shoulder blades of the dog regardless of the size of the animal. After the first treatment infertility is achieved within 6 weeks and lasts for at least 6 months. During the first 6 weeks dogs should be separated from bitches in oestrus. This is not necessary for any further re-implantations.

The period between implantation and testosterone levels being suppressed (<0.4 ng/ml) varies from dog to dog. The majority of dogs are below the threshold between 7-28 days, with some as long as 49 days. In clinical trials, all dogs administered Suprelorin® at six-month intervals remained infertile.

Suprelorin® is used for different purposes in different countries. This seems to depend on attitudes to surgery for neutering in general and the number of un-neutered pets in the dog population as well as the use in stud dogs.

In countries like the UK, where neutering of male puppies at 6 months of age is routine, the implant is used mostly in older non-neutered males where the owner wants to avoid surgery or by breeders with several stud dogs to avoid aggression between males. Suprelorin® can be used to monitor the effect of castration on the male before performing irreversible surgery. In kennels with several entire males the implant can be used to suppress testosterone in the males that are not being used for stud work at any particular time.

In Scandinavian countries where neutering of males is not performed routinely, as it is against animal welfare legislation, Suprelorin® is used more often to pharmacologically castrate males. The implant can be given routinely every six months or when the increase in testicular size indicates that it has stopped working.

Caution of use
The decrease in testicular size is sometimes noted by owners showing dogs. In some cases hair loss seems to occur, which does come back after the implant has stopped working.

More than 75% percent of dogs return to normal plasma testosterone levels within one year after administration of their final implant. Viable sperm are seen approximately 9 weeks post testosterone recovery (Johnston et al. 2001). This is generally between eight and ten months post the last implantation.
The variability in the period of suppression cannot be attributed to any particular feature. Timing of recovery depends on the patient’s individual sensitivity to the active ingredient.

Conclusion:
Suprelorin® is a valuable alternative for surgical castration. Although normal male fertility should return within 12 months of use, more data are needed for its use in very valuable stud dogs.

Abstract
Objectionable behaviour, such as roaming, inter- and intraspecific dominance, urine marking and mounting is an important reason for owners to present their dog for orchiectomy(1).

However, the outcome of orchiectomy with respect to altering this behaviour is not always clear-cut(2) and thus sometimes unsatisfactory for the owner. Furthermore, orchiectomy may be followed by side effects of which an increase in bodyweight and decreased physical activity are the most important examples(3). For these reasons clients may be reluctant to apply an irreversible treatment of which the outcome is uncertain and which is often considered to be detrimental to the dogs’ integrity. So far, a reversible and representative alternative to castration is not available to perform a trial treatment of these dogs. Such a trial treatment would be useful to find out whether the effects of orchiectomy in an individual dog are satisfactory for an owner or not, after which a more well-founded decision can be made to perform orchiectomy.

The changes in sexual behaviour after orchiectomy in male dogs have been ascribed to the decrease of plasma testosterone concentration. However, the relationship between androgens and sexual dimorphic behaviour is not robustly causal, evidenced by the variable effect of orchiectomy on behaviour. Probably, the lack of predictability is caused by the fact that mainly the secondary (consummatory) rather than the primary phase (courship) of normal sexual behaviour decreases after orchiectomy(3).

For some time now implants slowly releasing the GnRH-agonist deslorelin (4,7 mg deslorelin / implant, Suprelorin®) have been available to veterinarians in Europe. These implants induce a decrease of the basal plasma testosterone concentration in dogs within 6 weeks after administration. This decrease of plasma testosterone concentration inhibits spermatogenesis which results in infertility for at least 6 months (Suprelorin®). Reversible induction of infertility is therefore the indication for which these implants are registered in Europe. A study in ferrets with GnRH-agonists showed significant effects on some behavioural parameters, where among sexual behaviour, inter-specific aggression and play behaviour(4). Our hypothesis is that deslorelin implants will be suitable to serve as a trial treatment to explore the behavioural effects of orchiectomy in an individual dog.

Animals and methods
A pilot study (PS) was performed from March 2006 tot July 2008 in which we made use of questionnaires and spontaneous feedback of owners to assess the behavioural effect of deslorelin implants in 21 dogs (4,7 mg, n=8; 9,4 mg, n=13, Suprelorin®). Median age of the dogs at onset of the study was 2,1 years (range: 8 months to 5 years).

Afterwards we conducted a comparative study (CS), that started in November 2008 and which is still ongoing. In the latter study we compare dogs that are castrated surgically with dogs that are implanted. It was choice of the owner
Jeffrey de Gier

Interestingly, some dogs in PS and CG showed a temporary increase of one of their problem behaviours: mounting, urine marking, and intermale dominance (fig. 1)(1, 2). Information on the following 4 owner-experienced problem behaviours was collected in both PS and CS with the use of a questionnaire addressing the changes in mounting, roaming, intermale dominance and urine marking (leg lifting). Furthermore, changes in playfulness and balanoposthitis, if present, were recorded. Preliminary results from the questionnaire-based survey will be presented here but not results of the behavioural tests as the study is ongoing and these results have not been analysed yet. For the different behaviours, owners were asked whether there was any change or not. If so, owners could report deterioration or improvement. For the latter, in CS, we asked if the improvement was < 50%, > 50% or > 90%.

Plasma testosterone concentration was measured in plasma samples by a RIA (Coat-A-Count®, Total Testosterone, Diagnostic Product Corporation, Los Angeles, CA, USA) as previously described(5). The lower limit of quantitation was set at the lowest standard point (51 pmol / l).

Results & discussion

In all dogs in the CS a significant decrease of the plasma testosterone concentration was observed. Median plasma testosterone concentration before and 4-5 months after treatment were 11.0 x 103 and 72.5 [pmol/L] respectively in CG (n=24) and 18.5 x 103 and below the detection limit of 51 [pmol/L] respectively in SG (n=5). These results are in accordance with the literature(6, 7). If the total percentage of improving dogs in PS is compared to the literature and in the CS CG is compared to SG, we found similar changes for 3 problem behaviours: mounting, urine marking, and intermale dominance (fig. 1)(1, 2). Roaming showed much more improvement in the CS compared to PS. This can be explained by the fact that, in PS, many owners stated that roaming had never been problem behaviour for their dog before and after treatment. When addressing all 4 investigated problem behaviours more than half of the dogs that were said to have improved by the owner showed a marked improvement of more than 50% (fig. 1), which is comparable to findings by Neilson et al. (1997) who studied dogs after surgical castration(2). Playfulness increased in approximately 40% of dogs, but only in approximately 20% this increase was perceived as more than 50% by the owners. Interestingly, some dogs in PS and CG showed a temporary increase of one of the four problem behaviours during the first days after implantation. This can probably be explained by the initial increase of plasma testosterone concentration which is caused by the deslorelin implant(3). Changes in problem behaviour and plasma testosterone concentrations of the implanted and castrated dogs as reported by the owners that have been analysed so far in this study are similar and in accordance with previous findings regarding surgically and chemically castrated dogs in literature(1, 2, 7). Therefore, implants containing 4,7 mg deslorelin (Suprelorin®) probably accurately predict behavioural changes that can be expected after surgical castration in individual dogs.

Literature:

The use of Suprelorin® in tom cats and queens

Why downregulation?
Alternatives to surgical castration in cats may be requested for cats intended for breeding purposes and for cats with increased anaesthetic risk due to age, heart or kidney insufficiency. However, control of pet overpopulation, especially of free-ranging cats, is necessary and behaviour of intact male and females (straying, increased vocalisation, urine marking etc.) may negatively influence the relationship to the owner which makes him/her seeking for suppression of sexual behaviour and reproduction control. Slow release GnRH agonist implants like Suprelorin® offer a promising alternative inducing all castration-related effects without surgery in tom cats and queens.

Application of Suprelorin® in toms
Following implantation of Suprelorin®, mean testosterone (T) concentrations are significantly reduced within 28 days. Already on day 20, mean T concentrations are < 0.1 ng/mL (below the detection limit of the T test) with an extent of inhibition of already 98% of pre-treatment T values. Full downregulation as indicated by T < 0.1 ng/mL is achieved earliest 20 days (5/10 toms) and latest eleven weeks after implantation (9/10 toms).

In our study, full downregulation was delayed in one tom until week 27, although all castration-related side effects were observed in this respective tom and T concentrations varied between 0.1 – 0.2 ng/mL from day 20 on. As in the dog, testis size is an excellent marker for ceasing of T production in most toms. Compared to pre-treatment values, mean testicular size is decreased by approximately 21% already on week 4 and more than 50% from week 12 on. Besides, penile spines disappeared as in surgically castrated cats. All castration-related side effects may be observed following successful downregulation and ceased T production: A significant increase of food intake of toms can be observed and therefore restricted instead of ad libidum feeding is recommended as in surgically castrated toms to avoid excessive weight gain. Besides, urine marking stopped or at least significantly decreased. Following an initial increase, sexual behaviour, mounting, libido, mating, is significantly reduced in treated toms after 11 -16 weeks; however, mounting can be observed after excessive animation of a teaser queen. Toms get temporary infertile after treatment; however, infertility may be delayed by about 6 weeks after successful downregulation as duration of spermatogenesis is 46.8 days in toms.

Like in the dog, all effects are fully reversible. Duration of efficacy – as observed from clinical experiences – varies between six and 24 months. Recrudescence of spermatogenesis until pre-treatment semen quality may take up to five - six months whereas first spermatozoa can be expected after five to nine weeks.

Application of Suprelorin® in queens
The use of GnRH agonist implants for temporary suppression of ovarian function has been successfully described in queens. Queens can be implanted either in seasonal anoestrus, in oestrus or in interoestrus periods. In seasonal anoestrus, oestrus induction following implantation is probable. An initial stimulation measured by an increase of estradiol-17β (E2) concentrations after implantation is commonly observed in oestrus and interoestrous cats; however, oestrus induction is rare in those cases, but possible. It is important to keep in mind that all induced oestrous may be fertile, so mating should be avoided. If mating resulted in pregnancy abortion may be possible then, but successful termination of pregnancy is also possible. Following the initial increase of E2 and also of progesterone (P4) concentrations, hormone concentrations started to decrease 2-4 weeks after implantation in treated queens. A temporary increase of E2 with or without oestrous signs may be observed during the effective treatment and is followed by phases without sexual activity indicating that treatment is still effective. As in the tom, all other castration-related side effects like increased food intake can be observed in queens, too.

The duration of efficacy, i.e. suppression of oestrous symptoms, varies between six and 24 months. Interestingly, injection of a second implant during effective oestrus suppression (a temporary increase of E2 was observed in 1/10 cats, therefore 5/10 were implanted again) does not influence the duration of efficacy (one implant: 11.1 ± 2.9 months versus two implants: 11.0 ± 2.3 months).

Until now no data about the reversibility of treatment induced effects has been published strongly indicating that breeders have to be informed about this before implantation. However, it could be shown that after the end of efficacy ovarian weight and uterine diameter are similar to untreated controls. Besides, own observations restricted to some clinical cases show that queens that are mated following treatment in naturally occurring oestrous conceived and delivered healthy kitten. Further data are necessary to finally verify these observations.

Another option – Urine marking
Own observations show that GnRH agonist implants can effectively suppress excessive urine marking in surgically neutered toms and queens. This could be verified by several practitioners. Bacterial cystitis should be excluded before treatment. Although the mode of action is not fully understood, implantation of Suprelorin® offers an interesting therapeutical possibility.

General comments
Sedation or anaesthesia is not necessary for implantation; it is well tolerated by all cats. Following implantation, normally no local reaction (swelling,
scratching etc.), no major or minor treatment related negative side effects are observed. In those cases when the owners want to breed a tom or a cat although the GnRH agonist implant may still effectively suppress reproduction, implantation in the umbilical area should be preferred to implantation between the shoulders. However, as Suprelorin® is not licensed for the use in cats at the moment, the pet owner has to be informed about the mode of action, the delay between implantation and efficient hormonal castration and the variable duration of efficacy before implantation. Then Suprelorin® is a promising alternative for oestrus suppression and reproduction control in male and female cats.

References are available from the authors.

Contact: Dr. Sandra Goericke-Pesch
Clinic for Obstetrics, Gynecology and Andrology of Large and Small Animals with Veterinary Ambulance,
Justus-Liebig-University
Frankfurter Str. 106
35392 Gießen
sandra.pesch@vetmed.uni-giessen.de

Use of deslorelin to control fertility in the bitch.

Since deslorelin implants (Suprelorin®4.7mg, Virbac, Carros, France) were available on the veterinary market, the will to use them in bitches in our routine practice has become more and more intense. Indeed, its two step mechanism permitted by the daily delivery of the GnRH agonist compound may allow activation and inhibition of the oestrous cycle, which both find clinical applications in our everyday activity, from oestrus induction to chemical sterilization. From a scientific background however, data concerning these different uses were mainly restricted to experimental bitches (Trigg et al. 2001; Kutzler 2005) and yet no clear guidelines concerning the use of this product in females has been edicted. We started studying these aspects in March 2009 and from now, implanted 73 individuals of different size and breed (44 of them for chemical sterilization and 29 of them for oestrus induction), giving us a wide clinical overview of what practitioners may expect from these uses in the field.

Implant administration in the bitch: our recommendations.

When starting these studies, we did not know what to expect and therefore, on the contrary to the male dog, we decided to administer the implant subcutaneously in the umbilical area. Indeed, this location was allowing easier removal, which might be necessary when 1) a side effect related to this treatment is suspected, and 2) as described by Kutzler et al (2005), to avoid premature downregulation of the pituitary when used for oestrus induction. In our experience, it has always been easy to find and locate by palpation, provided it has been implanted just below the skin. We also reported no migration in the treated bitches.

“Flare up” effect: clinical aspects and subsequent recommendations.

Depending of the stage of the cycle, bitches will exhibit different responses to administration of deslorelin implants. When implanted at any stage of anoestrus, 46/47 bitches (97.8%) expressed an induced oestrus in the week following implantation. In 40 bitches, time from implantation to oestrus induction was 4.2±1.4 days [2 to 7 days after]. 30 days after, 43/47 bitches (91.5%) did not exhibit oestrous signs anymore. Anovulatory cycle was reported in 16/47 bitches (34%), but no statistical difference could be enlighten to discriminate the ones that ovulated and the ones that do not. Oestrus induction also concerned 5/14 bitches (28%) implanted in diestrus, characterized by presence of vulvar swelling, vulvar discharge and keratinized cells on the vaginal smears. When observed, implants were removed, as concomitant high levels of progesterone and estrogens may have favored occurrence of uterine disorders. In some of these diestrous bitches, oestrus was induced with progesterone levels >60 ng/mL, which was different from the threshold proposed by Trigg et al (2001), who did not experience oestrus induction when bitches were above 5 ng/mL. 10 bitches were also implanted in oestrus (before ovulation) and in all these last ones, no more oestrus signs
were exhibited 30 days after implantation. Anovulatory cycle was also reported in 4 of these bitches. Therefore, if in the purpose of oestrus induction it is clear that bitches should be implanted in anoestrus, when looking for chemical neutering, it is less evident to define the optimal implantation time. Diestrus has been proposed in the past (Trigg & Yeates 2008; Romagnoli et al. 2009), but the data we have let us think that due to the deleterious effects which might be encountered, implanting during oestrus may be more effective. Development of medical protocols to avoid the induced oestrus may change this, but to date, none of the attempts have been successful to define an optimal solution (Wright et al. 2001; Corrada et al. 2006).

**Chemical neutering: monitoring is important.**

5 bitches implanted in anoestrus presented persistent heats which lasts more than 30 days. In only two cases, it was related to the presence of ovarian cysts and the bitches were surgically neutered. In the three others, no ovarian abnormalities were observed and after implant removal, oestrous signs ceased after 1 week. Therefore, implanted bitches should be controlled after 30 days to ensure that heats are over and if not, ultrasound examination of the genital tract is advised to rule out the presence of ovarian cysts. To date, we do not have enough data concerning the length of efficacy of these implants but they may be similar to what was observed in the male. Indeed, return in heat was observed in only 5 bitches yet, between 6 and 10 months after implantation. 2 females were implanted for more than one year and still no oestrus sign has been observed.

**Oestrus induction: removal and monitoring of the subsequent luteal phase.**

When oestrus is induced, ovulation occurred 12±2 days after implantation. In our study concerning 29 bitches and on the contrary to what was reported by Kutzler et al (2005), we decided to remove it just after occurrence of ovulation (defined as progesterone level >5-6 ng/mL), as in preliminary trials we encountered several times anovulation when this was performed before. Anovulation was reported in 7/29 bitches (24%). In these bitches implants were removed 20 days post-implantation and heats ceased during the following week. After breeding, pregnancy was reported in 65% of the bitches and mean litter size obtained was 7.5±3.5 puppies. Luteal failure was suspected in 3 cases, one of which gave birth 58 days post-ovulation as the owner refused supplementation. When used for oestrus induction we would therefore strongly recommend performing a luteal phase following and progesterone supplementation should be instaured when progesterone levels drop below 10 ng/mL during the first 2/3 of pregnancy.

**Deslorelin implants offer great perspectives for the future in management and control of oestrus in bitches.** All bitches seem to respond in the same way, whatever the size and age, and from what we know now, the effects are more related to the hormonal environment. Several aspects (length of efficacy, protocols to avoid oestrus induction) still need to be defined but with a good knowledge of what to expect, their use in the female can be recommended.

**Bibliography:**


Use of deslorelin to control urinary incontinence in the bitch

Urinary incontinence (UI) is characterized by the involuntary loss of urine1. The risk of UI is less than 2% in intact bitches 2-5 but up to 20% in spayed dogs 3, 5-7. A direct relationship between UI and the removal of the ovaries was already conjectured in 19658 and was clearly demonstrated in 19859. It was generally assumed that UI after spaying is due to an estrogen deficiency, however several observations do not support the hypothesis that the lack of estrogen is the only reason for the development of UI. Removal of the ovaries results not only in estrogen deficiency but also in a chronic elevation in the production and secretion of FSH and LH10. Changes in the reproduction controlling hormones (GnRH, FSH and LH) after ovariectomy may play an important role in the pathophysiology of spay-induced UI, since receptors for LH, FSH and GnRH are present in the smooth muscle fibres and in the epithelium of the bladder and urethra11.

High doses of GnRH analogues administered in depot preparations for long term release are known to down-regulate GnRH receptors in the pituitary. The GnRH-treatment of spayed continent dogs had the desired effect of producing a long-term reduction of circulating gonadotropins to concentrations comparable to those of intact bitches during anestrus. Furthermore, the use of GnRH-depot analogues increased the bladder threshold in 9 of 10 spayed continent dogs, while the urethral pressure profile remained unchanged12.

Material and methods:

Eighteen spayed bitches (3 Boxers, 3 mixed-breed, 2 American Bulldogs, 2 Dalmatians, 2 Great Danes, 1 Akita Inu, 1 Bouvier des Flandres, 1 Bull Mastiff, 1 Dobermann, 1 Luzemer Laufhund, 1 Irish Setter) with spay-induced UI were included in this study. The diagnosis was established by ruling out all other known causes of urinary incontinence. Clinical examination, urinalysis, haematology and serum biochemistry were normal, the results of the urine culture were negative. At presentation the mean age was 7.5 ± 3.4 years and the duration of incontinence was 1.9 ± 1.2 years. The body weight varied between 19 and 60 kg (35 ± 12 kg).

All animals were treated with Deslorelin acetate (DA) 4.7mg or 9.4mg subcutaneously. Dogs with a body weight below 30 kg received one implant, while larger dogs received two implants. Dogs were treated three times and three dogs were treated 4 times, 7 times and 11 times respectively.

Results:

Complete continence was achieved in 9 dogs after GnRH-treatment. The mean duration of continence after one treatment was 265 ±184 days. The longest period of continence after repeated treatments was observed in an American Bulldog. This dog was treated 11 times since 1999 and is still continent and under treatment. One boxer was treated seven times; she was continent under treatment for 5.5 years until her death at the age of 12.5 years, due to reasons unrelated with the urogenital tract. Another American Bulldog was treated 3 times; she is still continent and still under treatment. An Akita Inu having had sebaceous adenitis and spayed induced UI was treated successfully twice. Five dogs were continent after the first treatment, however two of them only for 21 and 68 days, respectively. In those two dogs the treatment was repeated without success, one of those dogs had osteosarcoma and was euthanized 5 weeks after the second treatment. One boxer, which responded to the first treatment with continence for 576 days, developed cystitis. After curing the cystitis with antibiotics the treatment was changed to twice daily application of PPA.

In six dogs there was an improvement of the continence after implantation of DA. The owner of one was satisfied with this result and the dog was treated four times with DA. In the remaining 5 dogs a combined treatment with α-adrenergic drugs restored continence. Three of these 5 dogs had previously failed to respond with α-adrenergics alone. Three dogs did not respond to GnRH-treatment. One had a heart problem and was euthanized. One of the remaining two dogs became continent with an additional treatment with α-adrenergics.

In the other there was only a partial success, with a reduction of the frequency and the amount of urine lost at each episode. However, both dogs had already responded to α-adrenergic treatment before with continence or improvement, respectively. No side effects were observed.

Conclusion:

The therapeutic effect of DA is inferior to conventional medications, such as α-adrenergics. However, due to the long-acting effect of DA, there is greater convenience and a reduced commitment by the owner. Furthermore with DA alone or in combination, continence was restored in dogs that failed to respond to α-adrenergic therapy alone.

References

Alternative for surgical castration in ferrets

Surgical castration of ferrets (Mustela putorius furo) is common practice in the USA and various European countries. Although in male pet ferrets (hobs) there is no medical need for castration, they are mainly castrated to prevent reproduction, to reduce interspecies aggression enabling them to be kept in groups, and to decrease the intensity of the musky odor produced by the sebaceous glands.3

Hyperadrenocorticism is a common disease in neutered pet ferrets. The syndrome differs from hyperadrenocorticism in other species, such as humans and dogs, in that glucocorticoid excess is much less pronounced in ferrets. Instead, in ferrets the disease is characterized by excessive adrenal production of sex steroids, giving rise to vulvar swelling in neutered female ferrets (jills), recurrence of sexual behavior in neutered hobs, and alopecia.1 It has been hypothesized that increased concentrations of gonadotropins, which occur after neutering due to the loss of negative feedback, persistently stimulate the adrenal cortex resulting in adrenocortical hyperplasia and tumor formation. Strong support for this hypothesis may be found in the fact that the depot GnRH-agonists, leuprolide acetate and deslorelin, can be used successfully to treat ferrets with hyperadrenocorticism,2,3 and that LH-receptors (LH-R) have been detected in the adrenal glands of ferrets with hyperadrenocorticism. These receptors were considered to be functional because plasma concentrations of adrenal androgens increased after intravenous injection of a GnRH-agonist.4 Based on these findings it has been proposed to search for alternatives for surgical castration in ferrets. One of the possible alternatives for surgical castration is the continuous administration of a GnRH analogue. The results of the use of these analogues differ, however, among the different species. In dogs and cheetahs continuous administration of a GnRH analogue suppresses spermatogenesis. In the bull, however, continuous administration of a GnRH analogue leads to basal LH concentrations which are higher than in control animals, possibly explaining their concurrent increased plasma testosterone concentrations. In addition, testis volume is also increased, and more round spermatids were found in the seminiferous tubules. In marmoset monkeys and wallabies plasma testosterone concentrations remain within the normal range during the use of a long-acting GnRH agonist.5

In search for a suitable alternative two studies were performed. The initial study was carried out with male ferrets, kept under laboratory conditions, to evaluate whether the deslorelin implant would be suitable as alternative for surgical castration. In this study the effect of treatment with the depot GnRH-agonist implant, containing 9.4 mg deslorelin, on plasma testosterone and gonadotropin concentrations and concurrent testes size, spermatogenesis, the typical musky odor, and the interspecies aggression and sexual behavior was investigated. Twenty intact hobs (1 - 2 yrs of age) were divided into 3 groups. Ferrets from Group 1 (n=7) were surgically castrated. Ferrets from Group 2 (n=7) were given a deslorelin implant, while

ferrets from Group 3 (n=6) received a placebo implant. Plasma testosterone concentrations were below the detection limit of the assay in the ferrets with the deslorelin implants. The testis size in these ferrets was also very small compared to those from group 3. As expected, plasma LH and FSH concentrations rose significantly in the surgically castrated ferrets compared to the intact ferrets, while in the ferrets with the deslorelin implants a decrease in concentrations was seen. According to a human test panel, ferrets which had received the deslorelin implant smelled the least. Normal germ cells were found in the testes from the ferrets with the placebo implants, while no normal germ cells could be found in the testis from the delorelin group. Finally, ferrets from the deslorelin group showed less agonistic behavior compared to the ferrets from the surgically castrated group and those from the placebo group during confrontations test. The ferrets from the deslorelin group also showed less neckgripping. The deslorelin implant therefore addresses all issues related to the desire to surgically castrate male ferrets, and can be seen as a suitable alternative for surgical castration in ferrets.6,7

Based on the study described above we felt confident to perform a second study in which Suprelorin6® (a implant containing 4.7 mg deslorelin) was given to 72 male and 60 female privately owned ferrets. The effect of the implant was evaluated over a period of 2 years. The great majority of owners was very satisfied with the effect of the implant. The implant seems to work for 2 years in ferrets, but the results need some further evaluation. During this study, it was also evaluated whether an oral dose of 2 mg medroxyprogesteron acetate given 2 days prior to placement of the Suprelorin6® implant would prevent estrus. The turned out, not to be the case. Estrus duration after implantation was usually no longer than 2 weeks, which was considered acceptable by the owners. Based on the above finding we conclude that Suprelorin6® can be considered a suitable alternative for surgical castration in ferrets. Whether the implant indeed reduces the incidence of adrenal disease in ferrets needs further investigation.

References