

Use of a Gonadotropin Releasing Hormone Agonist Implant Containing 4.7 mg Deslorelin for Medical Castration in Male Ferrets (*Mustela putorius furo*)

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ABSTRACT

Sterilization of ferrets (*Mustela putorius furo*) is a common practice. Male ferrets, unlike females, don't need castration for medical reasons, but are frequently neutered to prevent reproduction and reduce their musky odor and aggressive territorial behavior. The search for an alternative to surgical castration is an important goal and challenge in this species. The use of a gonadotropin releasing hormone (GnRH) agonist implant containing deslorelin in ferrets has been documented in the literature as a treatment for adrenocortical disease and, to a lesser extent,

for medical castration. This study is the first evaluation of a GnRH-agonist implant containing 4.7 mg deslorelin for medical castration in male ferrets with an assessment of the duration of infertility over a 3-year follow-up. Twenty-nine intact male ferrets in rut were implanted and were used for tolerance evaluation. Infertility was assessed in 27 ferrets by evaluating their testosterone concentrations, testis size and musky odor. Our results indicated that infertility was induced within 6 weeks post-implantation and that the suppression of fertility lasted at least 16 months. No side effects related to the implant were reported. The 4.7 mg deslorelin implant is a suitable alternative for surgical castration in male ferrets.

INTRODUCTION

Sterilization of male and female ferrets (*Mustela putorius furo*) is a common practice in Europe, USA, and Australia. Female ferrets (jills) that don't reproduce need to be neutered because they may develop a hyperestrogenism with a secondary pancytopenia and death in case of continuous estrus for a long period (> one month) (Goericke-Pesch & Wehrend, 2012, Proháczik *et al*, 2009). Male ferrets (hobs) do not need castration for medical reasons, but are frequently neutered to prevent reproduction, reduce the musky odor produced by their sebaceous glands and reduce aggressive territorial behavior (Schoemaker *et al*, 2008a, Vinke *et al*, 2008).

The role of surgical neutering in the development of hyperadrenocorticism in both sexes has already been described. Schoemaker *et al* (2000) showed a correlation between surgical neutering and hyperadrenocorticism in ferrets regardless of age. The mean interval between the age of neutering and the age at onset of hyperadrenocorticism in that study was 3.5 years. Hyperadrenocorticism is due to the loss of negative feedback from the gonads on the hypothalamus.

A secondary increased concentration of gonadotropins leads to a permanent stimulation of the adrenal glands. The resulting hyperadrenocorticism is due to hyperplasia or neoplasia of one or both adrenal glands (Chen *et al*, 2010, Chen *et al*, 2014). The use of a gonadotropin releasing hormone (GnRH) agonist implant containing deslorelin seems to be a safe and efficient way to control clinical signs associated with hyperadrenocorticism (Schoemaker *et al*, 2008b, Lennox & Wagner, 2012, Wagner *et al*, 2005, Wagner *et al*, 2009).

Alternatives to surgical neutering have been proposed to avoid the occurrence of hyperadrenocorticism.

The fertility of female ferrets has been successfully controlled with implants containing 4.7 mg of deslorelin (Goericke-Pesch & Wehrend, 2012, Proháczik *et al*, 2010).

Two previous studies evaluated the use

of a GnRH-agonist implant containing 9.4 mg deslorelin in hobs for medical castration. The first one, conducted by Schoemaker *et al* (2008a), presented this use as an alternative to surgical castration for the management of fertility. The second, conducted by Vinke *et al* (2008), presented the effect of surgical and chemical castration on intermale aggression, sexual behavior and play behavior in hobs.

To the authors' knowledge, the GnRH-agonist implant containing 4.7 mg deslorelin (Suprelorin[®], Virbac, Carros, France) has never been evaluated for the medical castration of privately owned male ferrets. The aim of the study was thus to evaluate its efficacy for the suppression of fertility, as measured by the reduction of testosterone concentration, testis volume and odor, and its duration of action. A second objective of the study aimed to evaluate the tolerance of the 4.7 mg deslorelin implants in intact male ferrets.

MATERIALS AND METHODS

This study was an open and multicentric study which was performed in four veterinary clinics in France from December 2010 to December 2013. The study was conducted in compliance with the Guideline on Good Clinical Practices (VICH 2000). Owners were properly informed about treatment possibilities.

The onset of the contraceptive effect was assessed by observation of the ferret behavior, blood testosterone dosage, and testis measurement. The study ended upon return of sexual behavior or in December 2013. This study gave information on the onset of action, the duration of the infertility, and the tolerance of the product in male ferrets.

Animals

Privately owned, intact male ferrets under 3 years of age were included. The ferrets did not have previous deslorelin implants, corticoid within the preceding 14 days, concomitant disorders, or chronic or progressive disease. The ferrets were in good health (confirmed by the clinical examination and

the haematological and biochemical blood analysis results at the first visit).

Ferrets presenting with at least one of the following criteria after administration of deslorelin implant were withdrawn from the study:

- adverse event or concomitant disorder requiring an end to the follow-up
- concomitant disorder that may interfere with the testosterone dosage and/or the behavioral observations
- concomitant treatments likely to interfere with the product efficacy evaluation
- failure of compliance to the protocol by the owner, at least one testosterone dosage result missing, or
- withdrawal of the owner's consent.

Procedures

Study design

The first visit (V1) occurred during the winter 2010-2011 (December 13th 2010 – April 13th 2011). The second visit (V2) took place 42 +/- 2 days after the V1 and the third visit (V3) was in June 2011 (Figure 1). Depending on the date of V1, the V3 was between 67 and 198 days after V1 with an average of 138.14 days (approximately 4.5 months).

At each visit, the investigators performed a clinical examination, took blood samples, recorded the right testis measurement, and checked for possible adverse

events and concomitant treatments since the last visit.

The following clinical parameters were observed at each visit:

- general health (assessment of body condition, oral cavity, eyes, ears, skin and coat, heart, lungs, lymph nodes and spleen, digestive system and musculoskeletal system)
- evaluation of the injection site of the deslorelin implant
- seborrhea
- body weight
- temperature
- right testis width and length

The observations by the owner of the sexual activity of their ferret were recorded by the investigator at the time of the visits. At each visit, the sexual status of the ferret was recorded as being in rut or not in rut by the investigators based on these parameters: musky odor, seborrhea, urine marking, and aggressiveness.

The follow-up of each ferret ended upon return of sexual behaviour or in December 2013 when the owners were called in order to assess the return to fertility.

Treatment

The implants used were a slow-release device and contained 4.7 mg deslorelin acetate (Suprelorin[®], Virbac, Carros, France).

The implants were subcutaneously

Figure 1: Study design V: visit, D: day (*): V2b was optional: if sexual behaviour was still observed at V2 and/or blood testosterone level had not decreased between V1 and V2, a new visit (V2b) was scheduled 2 weeks after V2.

V1 :	D0	Inclusion Clinical examination Blood sample Injection of 4.7 mg deslorelin implant
V2 :	D42 ± 2 days	Clinical examination Blood sample
V2b* (optional):	D56 ± 2 days	Clinical examination Blood sample
V3:	June 2011	Clinical examination Blood sample

placed in the scruff of the neck (interscapular space or to the right or left side), using the implanting device provided with the implants. One implant per ferret was placed irrespective of the weight of the animal. All ferrets but one were anesthetized with isoflurane (Forene, Abbott France SA, Rungis, France or Belamont isoflurane, Nicholas Piramal Limited, London, UK) to ensure a good implant injection.

Blood collection

At each visit, one blood sample of about 1.5-2 ml was collected in a heparinized tube. If necessary the animals were anesthetized with isoflurane. Blood samples were collected from the jugular vein or the *vena cava cranialis*. The investigator gently shook the heparinized tube, filled in the Samples Identification form and then centrifuged the heparinized tube to obtain plasma and put it into another tube.

Testis measurement

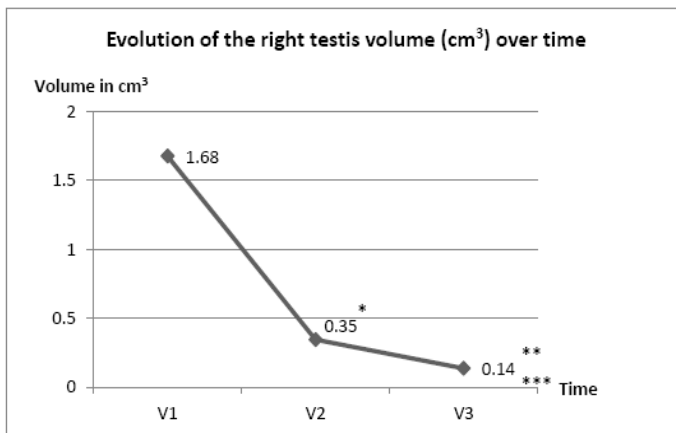
At each visit, the size of the right testis (width and length) was measured with a slide caliper.

The testis volume was calculated using the following formula: (width)² x length x 0.524 (in cm), as previously used in testis measurements of black footed ferrets (*Mustela nigripes*) in the study of Wolf *et al* (2000).

Hormone Analysis

The testosterone analysis of the blood samples was performed at VEBIOTEL laboratory (Arcueil, France). They used an automated quantitative test on PLC VIDAS® (Biomerieux, Craponne, France) by the ELFA technique (Enzyme Linked Fluorescent Assay). The lower limit of quantification (LLOQ) of the method was 0.1 ng/ml and the upper limit of quantification (ULOQ) was 13 ng/ml. For analysis, plasma testosterone values higher than the ULOQ

Figure 2: Evolution of the right testis volume (cm³) over time. * $p=5.63E-7$ between V1 and V2, ** $p=5.63E-7$ between V1 and V3, *** $p=2.3E-5$ between V2 and V3.



were considered as being 13 ng/ml and plasma testosterone values below the LLOQ were considered as being 0.1 ng/ml.

Statistics

All data were analyzed using the statistical software Statgraphics Centurion XV. The Normal Probability Plot, the Shapiro-Wilks test, as well as the standard skewedness and standardized kurtosis, showed that quantitative continuous variables (right testis volume and plasma testosterone level) had a distribution that presented a departure from normality, which tended to invalidate the Student Test. Therefore, the non-parametric sign test for paired samples was used for comparisons between the different time points. $P < 0.05$ was considered significant. For the analysis of the duration of efficacy of the deslorelin implant, a survival curve using the Kaplan and Meier method was generated.

RESULTS

Population Included

Twenty-nine male ferrets in rut were included and constituted the Intent To Treat population (ITT population). Two ferrets were excluded during the study. One was excluded because a blood collection was lost and another one died from a digestive illness. The other 27 ferrets included were kept for the efficacy analysis (Per Protocol

population: PP population).

Twenty-three (85.2%) were polecat-colored ferrets and 4 (14.8%) were albinos. At the beginning of the study, the mean age was 342.5 days +/- 187.6 days [181 days - 998 days] (median = 281 days) and the mean bodyweight was 1.6 kg +/- 0.4kg [0.8 kg - 2.5 kg] (median = 1.6 kg).

All the ferrets were privately owned, indoor housed and spent between 0.5 to 24 hours per day out of their cages. The number of animals in each house varied from 1 to 10. Eight ferrets (29.6%) lived alone, 4 ferrets (14.8%) lived with male ferret(s), 3 ferrets (11.1%) lived with female ferret(s) and 12 (44.4%) lived with male and female ferrets.

Testis Measurement

The volume of the right testis (Figure 2) decreased significantly between V1 (1.68 cm³ on average [0.63-3.4 cm³]) and V2 (0.35 cm³ on average [0.13-1.21 cm³] p<0.001) and continued to decrease significantly between V2 and V3 (0.14 cm³ on average [0.00- 0.52 cm³] p<0.001). Between V2 and V3, two ferrets had a small increase of this volume (from 0.15 to 0.38 cm³ and from 0.27 to 0.52 cm³). This increase was however not significant.

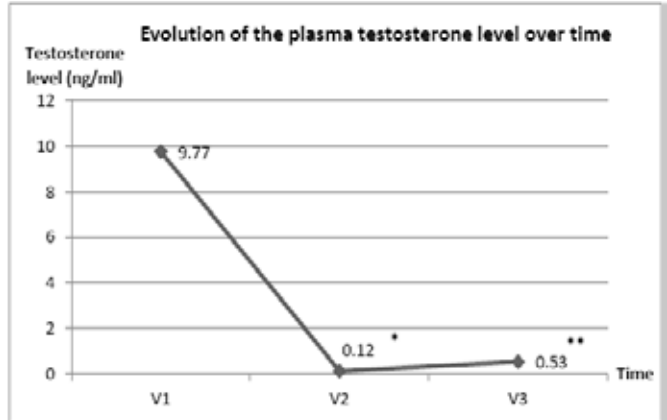
The testis volume was dramatically reduced between:

- V1 and V2 with a percentage decrease of 79.2%
- V1 and V3 with a percentage decrease of 91.7%
- V2 and V3 with a percentage decrease of 60.0%

Hormonal Changes and Sexual Behaviour

On D0, the plasma testosterone level was between 0.1 and 13 ng/ml with an average of 9.77 ng/ml (Figure 3) and all the ferrets were in rut.

Figure 3: Evolution of the plasma testosterone level over time. * $p=9.46E-7$ between V1 and V2, ** $p=3.86E-6$ between V1 and V3.



At V2, none of the 27 ferrets included in the study showed any manifestation of sexual behavior. Plasma testosterone was no longer detectable on at V2 (under LLOQ) for 25 ferrets (92.59%). Two other ferrets presented very low values, near the LLOQ (0.3 and 0.4 ng/ml).

The average plasma testosterone level for the 27 ferrets was 0.12 ng/ml and was significantly lower compared to D0 (p<0.001). The owners did not report sexual behaviour.

All these results showed that 6 weeks after deslorelin implant injection, the 27 ferrets were no longer in rut.

At the V3 visit, none of the 27 ferrets included in the study were in rut and the owners did not report sexual behavior. Plasma testosterone was not detectable at V3 for 19 ferrets (70.37%). The eight other ferrets had low values: five ferrets presented a plasma testosterone level at 0.2 ng/ml and three ferrets presented a plasma testosterone level of 0.4, 3.2 and 7.8 ng/ml respectively. The average plasma testosterone level for the 27 ferrets was 0.53 ng/ml and was significantly decreased compared to V1 (p<0.001) but not compared to V2 (p=0.182).

All these results showed that at V3 the 27 ferrets were still not in rut. The plasma testosterone levels were dramatically reduced between:

- V1 and V2 with a percentage decrease of 98.8%
- V1 and V3 with a percentage decrease of 94.6%

Duration of Efficacy

The date of return to fertility could be evaluated in 19 out of the 27 ferrets. It was not possible in 8 ferrets for the following reasons:

- Lost to follow-up for 5 ferrets
- Three ferrets had died since the V3 visit, on 04/17/2012 (approximately 10 months after V3), 06/01/2012 (approximately 1 year after V3), and 02/19/2013 (approximately 1 year and 8 months after V3), respectively.

By December 2013, nine ferrets had not yet shown a return to fertility. According to the owners, their ferrets did not present sexual behaviour or an increase in odor or testicle size. In those nine ferrets, the 4.7 mg deslorelin implant was still effective on average 2.87 years (approximately 2 years and 10 months) after implantation [2.69 years (2 years and 8 months) - 2.96 years (approximately 3 years)]. Ten ferrets showed a return to fertility before study termination. In those 10 ferrets, the average duration of efficacy of the deslorelin implant was 2.21 years (approximately 2 years and 3 months) [1.34 years - 2.89 years]. In the 19 ferrets for which data could be obtained the shortest

duration of action was 489 days (approximately 1 year and 4 months) and the longest follow up was 1080 days (approximately 3 years, ferret not yet returned to fertility).

In the survival analysis, the 27 ferrets were taken into account. The mean time to return to fertility was 936.88 (+/- 40.84) days (approximately 2 years and 7 months) (Figure 4).

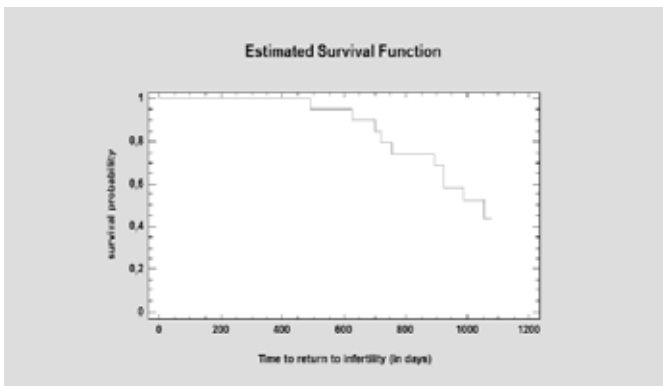
Side Effects

No local reaction occurred. Treatment-related negative side effects were not observed in the ITT population. Two ferrets were excluded during the study. One was excluded because a blood sample was lost and another one died from a digestive illness before V3. Neither of these ferrets were excluded for side effects related to the implants.

DISCUSSION

Deslorelin is a synthetic analogue of endogenously occurring gonadotropin-releasing hormone. The implants are a slow release device. Continuous release of a GnRH-agonist leads to an inhibition of the pituitary-gonad axis and an inability to synthesize or release the luteinizing hormone (LH) and follicle-stimulating hormone (FSH) responsible for maintaining fertility (Johnson, 2013). Deslorelin acetate implants are available in many countries in a 2.1, 4.7 and 9.4 mg dosage for use in mares, male dogs and ferrets.

Figure 4: Probability of remaining infertile for male ferrets implanted with 4.7 mg deslorelin implants (Kaplan-Meier curve).



The use of deslorelin implants in ferrets has been mainly documented in the literature as a treatment for adrenocortical disease and to a lesser extent for medical castration. In contrast to the two studies involving male ferrets implanted for medical castration (Schoemaker *et al*, 2008a, Vinke *et al* 2008), we included a large number of ferrets implanted from a wide range of ages and bodyweights.

In the study conducted

by Schoemaker *et al* (2008a), 21 hobs from 1 to 2 years old and weighing 1.4 +/- 0.2 kg (1.0-1.7 kg) were included. The ferrets were randomly divided into three groups of identical size and individually housed in outdoor cages at the Utrecht University, Holland. They were respectively surgically castrated (weight 1.4 +/- 0.2 kg (1.0-1.6 kg)), administered a 9.4 mg deslorelin implant (weight 1.5 +/- 0.1 kg (1.3-1.7 kg), 7 individuals) or administered a placebo implant (weight 1.5 +/- 0.1 kg (1.3-1.7 kg)). The data collected indicated that plasma testosterone concentrations, testis volume, spermatogenesis, and body odor in ferrets medically neutered decreased to a level equal to or even below those of surgically neutered animals. In the study published by Vinke *et al* in 2008 the effects of chemical and surgical castration on the occurrence of intermale aggression, sexual behavior and play behavior were examined in the same 21 male ferrets as the previous study.

In our study, 29 ferrets from 6 months to approximately 3 years of age and from 0.8 to 2.5 kg were implanted. We observed that the youngest ferret of the study was among the nine ferrets which did not return to fertility at the end of the study period. These ferrets were aged at the beginning of the study from 5 months and 28 days to 9 months and 19 days which is under the mean age (342.5 days). They weighed from 1.1 to 2.3 kg. Eight of them weighed more than the mean (1.6 kg). In contrast to the findings of Trigg *et al* (2006) who concluded that the duration of action of deslorelin implants was linked to the bodyweight of the implanted dogs, our findings could unfortunately not lead to any conclusion and especially to a correlation between the efficacy of the implant and the age and weight of implanted ferrets.

In two other published studies, the use of the 4.7 mg deslorelin implant has been evaluated in jills for medical neutering. Proháczik *et al* (2010) compared four treatments to suppress ovarian activity in 25 jills. The animals had a mean age of 1.5 years and a mean bodyweight of 760 g.

They were housed outside and divided into 5 equal groups (5 individuals per group). The authors observed that the deslorelin implant provided a long-lasting suppression of fertility of approximately 23 months. Goericke-Pesch and Wehrend (2012) presented the use of a GnRH-agonist implant containing 4.7 mg deslorelin for estrus suppression in seven jills. The animals were between 1 and 3 years old and weighed between 750 and 850 g at the beginning of the study. The results indicated that ovulation had occurred after implantation and that estrus remained suppressed within the observation period of up to 32 months.

The responses to treatment with deslorelin acetate implants of different dosages in ferrets with adrenocortical disease have been reported in several studies. Wagner *et al* in 2005 used 3 mg deslorelin acetate implants (not commercially available). Schoemaker *et al* (2008b) were the first to confirm a successful treatment of adrenocortical disease with a GnRH-agonist implant containing 9.4 mg deslorelin. GnRH-agonist implants containing 4.7 mg deslorelin were used in three studies for the management of adrenocortical disease (Proháczik *et al* 2009, Wagner *et al* 2009, Lennox and Wagner 2012). Those studies included between 1 (Schoemaker *et al* 2008b) and 35 ferrets (Lennox and Wagner 2012) of both sexes, various bodyweights and from 3 to 7 years of age. The duration of action of the implant for the control of clinical signs due to adrenocortical disease varied with the dosage of deslorelin (13.7 +/- 3.5 months with 3mg of deslorelin, more than 19 months, 17.6 +/- 5.0 months and 16.5 months with 4.7 mg of deslorelin and more than 2 years with 9.4 mg of deslorelin).

In our study, induction of infertility was assessed based upon evaluation of testis volume, plasma testosterone, and disappearance of sexual behavior. The duration of action of the implant was evaluated through the return of typical sexual behavior as assessed by the owner. It was shown that the testis volume and the plasma testosterone were

dramatically reduced between the different visits. Based on these results, correlated with the lack of sexual behaviour, the decrease of musky odor reported by owners and the absence of noticeable side effects, we believe that the 4.7 mg deslorelin implant is a suitable alternative to surgical castration in male ferrets. Based on similar methods and results, Schoemaker (2008b) came to the same conclusion with a 9.4 mg deslorelin implant.

The interest of our study is that it is the first evaluation of the duration of efficacy of the 4.7mg deslorelin implant in male ferrets (average 31 months [16 - 36 months]). This duration of action is consistent with the previous studies conducted with the 4.7 mg deslorelin implant used for the suppression of fertility in female ferrets (32 months, Goericke-Pesch and Wehrend 2012) or for the management of clinical signs due to adrenocortical disease (23 months, Prohácik *et al* 2010).

The various published studies are complementary and of great interest to evaluate the effectiveness of deslorelin implants in ferrets as an alternative to surgical castration. They all show that the two dosages of deslorelin implant are effective for medically neutering pet ferrets. At the time of submission of this article, we observed a duration of infertility of up to approximately 3 years. In the authors' experience, we have observed a duration of infertility of up to 5 years with the 4.7 mg dosage. At the time of submission of our study, the 9.4 mg deslorelin implant is the only dosage to be labelled for the suppression of fertility of male ferrets and no study has yet established the duration of action of this implant in ferrets. In dogs, the 9.4 mg deslorelin implant has a minimum duration of action for the suppression of fertility which is double that of the 4.7 mg one.

One could hypothesize that it should be the same for male ferrets. However, further studies would be of interest for evaluating the duration of activity for the 4.7 mg and 9.4 mg deslorelin implants and to establish if

there is a significant difference between the two dosages. It would also be interesting to further evaluate the efficacy of the implants with regards to a potential correlation with the age and weight of implanted ferrets.

CONCLUSION

Treatment with a GnRH-agonist slow-release implant containing 4.7 mg deslorelin is a suitable alternative for medical castration in male ferrets. Infertility is induced within 6 weeks and lasts at least 16 months. No noticeable side effects are observed in male ferrets following implantation with 4.7 mg deslorelin implants. Our study is complementary to those conducted with 9.4 mg deslorelin implants in hobs or with both dosages in jills. To the authors' knowledge, this is the first evaluation of a GnRH-agonist implant containing 4.7 mg deslorelin for medical castration in male ferrets with an assessment of the duration of infertility.

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