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FERTILITY CONTROL IN A MALE RABBIT USING A DESLORELIN IMPLANT. A CASE REPORT

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Abstract: Continuous low-dose release of the GnRH analogue deslorelin (Suprelorin, Peptech, Australia) causes a suppression of reproductive function in different species such as dogs, koalas, or kangaroos. No studies concerning the efficacy and safety in male rabbits have yet been conducted. A male rabbit with hypospadia was introduced to the Clinic for Animal Reproduction. The owner intended to keep it together with a fertile female rabbit. To avoid reproduction, a 4.7 mg deslorelin implant was injected subcutaneously. No negative reaction to implant placement was diagnosed by daily examination of the injection site for one week. To test the effectiveness of the treatment, blood samples were taken and the testes size was measured regularly. After an initial rise in testosterone levels for 14 d, a down regulation for seven month with values lower than 0.1 ng/mL was observed. In the same period, the size of the testes declined to 50 % of the original dimensions. Afterwards, both testes regained their former shape and size. Since it was not a stud rabbit, semen parameters were not determined. During the suppression of the reproductive function, no sexual activity was observed by the owners. These findings have yet to be proven by clinical trials with a sufficient number of animals, but this case indicates the efficacy of deslorelin implants in male rabbits.

Key Words: deslorelin, male rabbit, fertility control, contraception.

INTRODUCTION

Rabbits are increasingly kept as pets. Since rabbits are considered highly social creatures, many authors suggest keeping them in companion with another rabbit (Harcourt-Brown, 2004). Consequently, the owners often request neutering of one or both of the rabbits to prevent reproduction (More, 1999). Other reasons for neutering male rabbits are hypersexuality (e.g. attempts to mate the owner's legs), territory marking (spraying of urine or depositing faeces) and aggression against other rabbits or humans. Currently, male and – to a lower extent – female rabbits are neutered (spayed or castrated) surgically. A mortality rate of 1.4 per cent in rabbits undergoing anaesthesia (Brodbelt *et al*., 2008) and additional risks of intra- and post-operative complications have to be considered.

Some research-based recommendations on alternative, safe and effective techniques for prevention of reproduction in male rabbits have been published (Williams, 1980; Lohiyaa *et al*., 1999), but with unsatisfactory results. In general, tested strategies for anti-fertility agents for male animals that are long-

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acting, reliable and free of side effects have focused on administration of reproductive hormones and their analogues and on vaccination against antigens in the reproductive process (Trigg *et al.,* 2001).

Recently, slow-release biocompatible implants containing deslorelin have provided an opportunity for effective contraception for male dogs (Junaidi *et al.,* 2003), mice (Kher and Kalla, 1996), ferrets (Schoemaker *et al.,* 2008), koalas (Herbert *et al.,* 2001), Tammar wallabies (Herbert *et al.,* 2004) and other species. As yet, no adverse effects have been reported (Trigg *et al.,* 2006). Deslorelin is a D-Trp^{6}-Pro^{6}-des Gly^{10}GnRH analogue with two amino acid substitutions (Kutzler, 2007). Modification of the peptides results in an increase in resistance to peptidases and enhances receptor binding affinity. Thus, GnRH agonists have a longer half-life in circulation and are up to 200 times more potent than native GnRH (Herbert and Trigg, 2005).

Initially, long-acting GnRH agonists induce a significant increase in LH and FSH concentrations in male and female dogs, which can last for several days (Herbert and Trigg, 2005). Subsequently, the continued exposure to GnRH agonists suppresses the secretion of LH and FSH as a consequence of down regulation of GnRH receptors on gonadotrope cells of the pituitary (Hazum and Conn, 1988). Without the stimulating effect of FSH and LH, the gonads no longer produce gonadal steroids.

The deslorelin implant Suprelorin has been marketed since 2004 in Australia and New Zealand since 2005. It is formulated as a cylindrical implant in a preloaded syringe for subcutaneous implantation. In 2008, Suprelorin 4.7 mg was approved for use in male dogs in several European Union countries and is available via Virbac Animal Health (Carros Cedex, France).

To our knowledge, no studies concerning the efficacy and safety in male rabbits have yet been published.

MATERIALS AND METHODS

A 12 mo old male rabbit (breed: Loh rabbit) weighing 3.2 kg with a high-grade penile hypospadia was introduced to the Clinic for Animal Reproduction in spring 2008. Hypospadia is a defect of the urethra with a ventral opening in a line instead of an opening at the tip of the penis. It can be induced pharmacologically and genetic factors are likely to be involved in most cases (Kurzrock *et al.,* 2000). The owner intended to house it together with a fertile female rabbit but refused surgical castration.

To avoid reproduction, a 4.7 mg deslorelin Implant (Suprelorin, Peptech, North Ryde, Australia) was injected subcutaneously into the dorsal skin of the neck on April 7th 2008. Before treatment, an informed consent by the owner including the fact that the rabbit will not be suitable for human consumption was obtained and signed.

No negative reaction to the implant placement was diagnosed by daily examination of the injection site for one week. To estimate the efficacy of the treatment, repeated blood samples were taken in the first four weeks after administration and afterwards at monthly intervals. Blood was drawn from auricular vein or from vena cephalica. Serum was centrifuged at 1500 *g* and submitted to a commercial laboratory to determine testosterone concentrations by ECLIA (Elektrochemiluminescence Immunoassay, Cobas 6000, Roche Diagnostics, Rotkreuz, Switzerland). Furthermore, the size of the testes (including testis and epididymis) was measured regularly with a sliding calliper.

RESULTS

Serum testosterone concentration immediately before implantation of the bolus in May 2008 was 3.4 ng/mL, which is in agreement with the reference range of 0.4-4.6 ng/mL as reported by Artega *et al*. (2008). After an initial rise of testosterone concentration to 5.5 ng/mL, 9 d after the administration a temporary down regulation with values lower than 0.1 ng/mL was observed (Figure 1). In the same period, the length

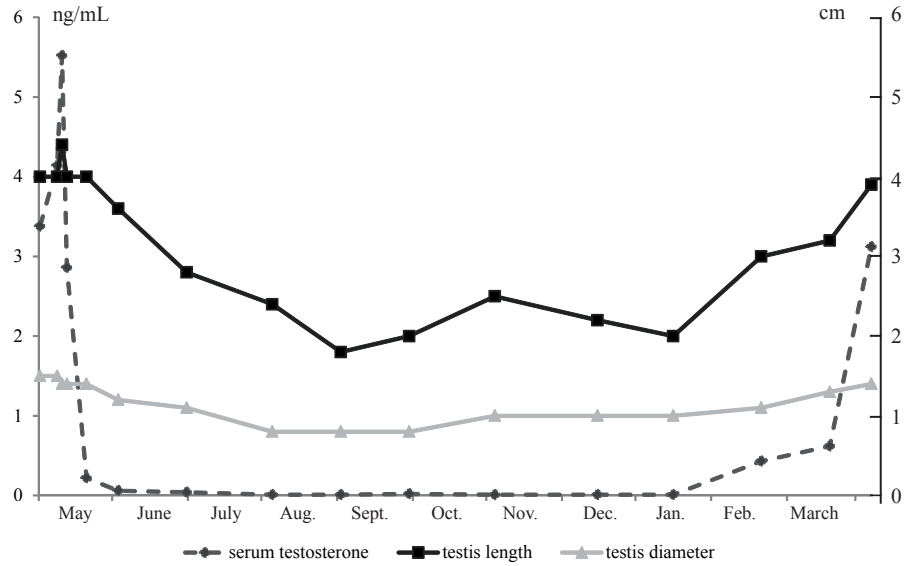

Figure 1: Testosterone concentration (ng/mL), testis length and diameter (cm) after implantation of 4.7 mg deslorelin.

of both testes (4.0 cm before administration of the deslorelin implant) declined to approximately 2.0 cm, which represents 50 % of the original dimensions.

After a period of 7 mo (June to December), the testosterone concentration increased again and reached 3.1 ng/mL in March 2009. Corresponding with the increase in testosterone concentrations, we observed a re-growth of the testes during the last 2 mo of the observation period. Length of the testes was 3.9 cm in March 2009. The diameter of the testes remained almost constant throughout the observation period.

Eight weeks after treatment, the male rabbit was co-housed with the female rabbit. During the suppression of the reproductive function, no sexual activity was observed by the owners and no offspring occurred. Since it was not a stud rabbit, semen parameters were not determined.

By the end of the observation period, the owner had changed his housing concept and consequently another injection was not necessary.

DISCUSSION

This case report indicates that the deslorelin implant was effective in decreasing testosterone concentrations to basal levels. Because semen parameters were not assessed, the effect of the deslorelin implant on fertility cannot be evaluated, but it is likely that the observed suppression of testosterone and decrease in testes size corresponded to a discontinued spermatogenesis. This effect of deslorelin implants has been demonstrated in dogs (Junaidi *et al.,* 2003), kangaroos (Herbert *et al.,* 2004), and other species. The co-housing with a fertile female rabbit did not result in undesired offspring. Regarding the subsequent increase in testosterone and re-growth of the testes, it can be presumed that semen characteristics had recovered completely. The complete recovery of male fertility has been demonstrated in dogs (Junaidi *et al.,* 2003; Trigg *et al.,* 2006).

Surgical castration reduces testosterone-dependent aggression among males (Arteaga *et al.,* 2008), reduces the size and secretory activity of the chin gland, and reduces or eliminates territory marking (Girolami *et al.,* 1997). Hence, it seems that these conditions might also be influenced by administration of a deslorelin implant, with a consequent decline in serum testosterone concentrations.

We conclude that the single, slow-release implant containing 4.7 mg deslorelin caused a long-term, reversible suppression of sexual function in the male rabbit. It remains open whether this technique leads to a safe and complete suppression of reproductive function without a remaining risk of mating during the pharmacological activity of the implant. The authors received anecdotal information of non-efficacy of the implant in single cases. In order to make an evidence-based recommendation, efficacy, reliability and safety have to be proven by clinical trials with a sufficient number of animals.

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