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Long-Term-Release GnRH Agonists Postpone Puberty in Domestic Cats

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Contents

The aim of this study was to assess the efficacy and safety of deslorelin acetate implants on domestic queen puberty postponement. Thirty, 114.4 ± 12.7 days old, 1.5 ± 0.1 kg prepubertal crossbred female cats were included in this study. The animals were kept under a positive photoperiod and randomly assigned to deslorelin acetate 4.7 mg SC implants (n = 15) or to a non-treated control group (n = 15). The queens were followed up daily and weighed weekly until puberty. Vaginal cytology was also carried out three times a week. Puberty was diagnosed by the presence of the typical oestrous behaviour and vaginal cytology findings. At puberty, ovariectomy was performed and the gonads grossly described. Age (281.2 ± 21.6 vs 177.8 ± 10.8; $p < 0.01$) but not weight (2.6 ± 0.1 vs 2.5 ± 0.1; $p > 0.1$) at puberty differed between the deslorelin and control groups, respectively. One deslorelin-treated female showed an oestrous response and another showed clinical signs of pyometra after the implants. Deslorelin-treated ovaries appeared small, while control gonads were normal. It was concluded that long-term-release deslorelin, administered at approximately 50% adult body weight, postponed feline puberty without altering growing rate.

Introduction

Domestic cat is an extremely prolific species in which safe and efficient reproduction control has not been fully achieved yet. In this regard, traditional steroid contraception provokes many side effects (Johnston et al. 2001), while non-steroid hormones have a potential for safe feline reproduction control (Gobello 2007). Gonadotrophin-releasing hormone (GnRH) agonists have been produced by substitutions of amino acids in the native GnRH molecule presenting greater potency and longer half-life (Karten and Rivier 1986). Long-term-release formulations of these agonists are available in the human and veterinary market of most of the countries.

Prolonged administration of GnRH agonists acts through desensitization and down-regulation of the GnRH pituitary receptors. However, this procedure is initially preceded by an increased release of gonadotrophins which, in mature females, can result in an undesirable oestrous response. Thus, in this gender, the time window of agonists' administration appears crucial to prevent this side effect.

Long-term-release GnRH agonists have shown to postpone puberty in humans (Bertelloni and Mul 2008) and dogs (Rubion et al. 2006); however, their effect on feline species has not been assessed yet. In prepubertal rats, suppression of gonadotrophins by GnRH analogues decreased ovarian weight (van den Dungen et al., 1989) and the number of large antral follicles (Muir et al. 1999).

Domestic cats normally achieve puberty at approximately 75% adult body weight (Johnston et al. 2001; Stamou and Boscos 2001). Therefore, under the speculation that at approximately 50% adult body weight there is a state of reproductive immaturity, we hypothesized that in female cats, the long-term-release GnRH agonist, deslorelin acetate, administered at this time point, postpones puberty, without the initial stimulation of the gonadal axis. The aim of this study was to assess the efficacy and safety of deslorelin acetate implants on domestic queen puberty postponement.

Materials and Methods

Animals

Thirty, 114.4 ± 12.7 days old, 1.5 ± 0.1 kg prepubertal crossbred female cats were included in this study during 1.5-year period. All the cats were born in our institutional cat colony, and five of them (17%) were littermates. The animals were kept under a positive photoperiod (14L : 10D) since birth, fed a commercial kitten food after weaning and given water *ad libitum*. The study was approved by the Faculty Institutional Care and Animal Use Committee (IACUC, Number 129/09).

Pharmaceutical protocols and follow-up

The females were randomly assigned to one of the following groups: deslorelin acetate 4.7 mg SC implants (Suprelorin, Virbac, France; n = 15) or a non-treated control group (n = 15). Deslorelin acetate (6-D-tryptophan-9-[N-ethyl-Lprolinamide]-10 desglycinamide) 4.7 mg implants were supplied in the form of biocompatible implants (0.23 × 15.2 mm) in preloaded disposable syringes for SC administration. The queens were followed up daily and weighed weekly until puberty (n = 29) or up to the age of 18 months if they had not reached puberty at that time (n = 1). Follow-up included physical examination and sexual behaviour observation (more than 1.5 h/day). Eventual appearance of clinical local or systemic side effects related to the treatments was also recorded. Vaginal cytology was carried out and interpreted as described by Mills et al. (1979), three times a week or whenever oestrous signs appear. Puberty was diagnosed by the appearance of the typical oestrous behaviour in the presence of a tom cat, which was taken to the females for this purpose, and more than 80 superficial squamous cells at vaginal cytology (Johnston et al. 2001; Mills et al. 1979). Post-implant oestrus response was defined when these signs appear within 2 weeks of implant administration (Gobello 2007).

Ovariectomy

Five to 15 days after puberty (n = 28) or at the age of 18 months, if puberty was not achieved (n = 1),

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ovariectomy was performed using the technique described by Janssens and Janssens (1991). One deslorelin-treated queen was not ovariectomized at puberty as the person who adopted it after the trial did not permit spaying. In the remaining animals, general anaesthesia was given with xylazine (1–3 mg/kg IM; Kensol, Köing, Argentina) and ketamine (15–25 mg/kg IM; Ketmin-50, Holliday, Argentina) and complemented with local anaesthesia using lidocaine 1% (maximum 0.5 ml). After surgery, ketoprofen (Ketofen, Fort Dodge, Argentina; 1 mg/kg) was injected SC (once) and then orally every 24 h during four additional days. The ovarian pairs collected during surgery were grossly assessed.

Statistical analysis

A descriptive statistics (mean ± SEM) was carried out, and age (days) and weight (kg) at puberty were compared between the groups using Student's *t*-test. Safety was analyzed using Fisher's exact test. The level of significance was set at $p < 0.05$ (SPSS 17.0, SPSS, Inc., Chicago, IL, USA).

Results

Puberty was achieved between the age of 180–428 and 134–286 days in the deslorelin and control groups, respectively. Age at puberty (281.2 ± 21.6 vs 177.8 ± 10.8; $p < 0.01$) but not weight at puberty (2.6 ± 0.1 vs 2.5 ± 0.1; $p > 0.1$) differed between the groups. One deslorelin-treated female did not achieve puberty during the period of the study, and this particular cat was considered an outlier and excluded from the previous mean. Another queen of the same group (6.7%) presented oestrous response 13 days after treatment. A third agonist-treated cat (the one which could not be spayed at the end of the study) showed clinical signs of pyometra 92 days after the implant. This female presented fever, purulent vaginal discharge and abdominal distension. The diagnosis was confirmed by ultrasound and immediately ovariohysterectomized. The remaining animals did not present any side effects during the study period ($p < 0.01$).

Discussion

In post-pubertal female cats, long-term-release GnRH agonists have shown to be effective contraceptives for periods exceeding 1 year (Munson et al. 2001; Rubion and Driancourt 2009). Conversely, in these immature animals, the puberty postponement obtained was, in general, shorter (approximately 100 days). These differences could be attributed to dose (4.7 vs 6 mg) or agonist (deslorelin vs azagly-nafarelin) used among the studies as well as to the dissimilar reproductive maturity of the experimental animals.

In the present study, there was also a wide range in puberty postponement among treated animals, and even one queen did not achieve puberty during the study period. This variability was previously described in dogs and cats treated with GnRH agonists (Janssens and Janssens 1991; Munson et al. 2001). Similarly, in mares, individual susceptibility to a single deslorelin application caused complete ovarian involution in some of the treated animals (Johnson et al. 2000).

Growing rate was not altered by the treatments as all the animals, independent of the group, reached puberty at a normal body weight. In line with our findings, there was also no effect of treatment on growth, based on sequential body weight data in pharmacologically gonadotrophin-depleted immature monkeys (Lunn et al. 1994).

The absence of post-implant oestrus response obtained in most (>93%) of the agonist-treated queens may reflex the immaturity of the ovaries and/or the hypothalamo-pituitary axis at this particular time point, that is, approximately 50% adult body weight. Similarly, prepubertal beagle dogs did not present post-GnRH agonist oestrous response when medicated at 4 months and 50% adult body weight (Rubion et al. 2006). For practical purposes, it therefore seems logical to indicate to avoid the peripubertal period when using depot formulations of GnRH agonists in domestic queens. The appearance of the oestrus response in only one experimental animal further represents individual variability to GnRH agonist effect in this species.

Pyometra 3 months after deslorelin implants was previously reported in an adult bitch (Corrada et al. 2006) although, up to the authors' knowledge, this is the first report in felids. It is worth noting that, in the present trial, the only cat that could not be spayed developed a pyometra. Therefore, the real incidence of this long-term side effect might be underestimated. Conversely, with the present information, no direct relation between the appearance of this disease and treatment could be confirmed. Finally, although it was beyond the objective of the present study, it would have been interesting to test fertility in these treated oestrous cats.

Conclusions

It was concluded that long-term-release deslorelin, administered at approximately 50% adult body weight, postponed feline puberty without altering growing rate. Although side effects appearance was low, they should be considered when using these implants.

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Conflict of interest

None of the authors have any conflict of interest to declare.

Author contributions

A. Risso realized the experiments and collaborates in the analysis and discussion of the results and the redaction of the manuscript. Y. Corrada participated in experiments elaboration and in the analysis and discussion of the results and the redaction of the manuscript. C. Barbeito collaborates in the results analysis and discussion of the results and the redaction of the manuscript. J. Diaz collaborates in the experiments and in the analysis of the results. C. Gobello, the director of the group, realized the experimental design and directed the analysis and discussion of results and the manuscript redaction.

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