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Medical contraception in cat: new and old drugs

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Abstract

Control of cat overpopulation is up until now has been a lost battle. The search for a cheap, reliable and easily applicable contraceptive covers a wide range of possibilities, but lately, very limited advances have been made. Main objective of drug-mediated fertility control in cats is to prevent reproduction (special concern to overpopulation) and to prevent estrus and male sexual behaviors in owned-cats and ultimately help management of catteries. There are 3 forms of delivery of contraceptive drugs in cats: tablets, injections, and implants. All contraceptive control discussed here is hormone-based, with a wide variation of possible side effects. Currently, there are no contraceptive methods that are 100% effective and each should be considered a temporary solution.

Keywords: Medical contraception, cats, progestin, melatonin, GnRH agonist

Introduction

Domestic cats are seasonal polyestrous species and long-day breeders with a positive photoperiod influence. Queens cycle repeatedly during the breeding season when melatonin concentrations are lower, unless interrupted by pregnancy or pseudopregnancy. Effect of seasonality is not very substantial for tomcat. Pathway to contraception is to reduce concentrations of gonadotropins (LH and FSH) leading to reduced concentrations of steroid hormones with an ultimate goal to prevent reproduction. Considering the reproductive physiology of domestic cat, to achieve contraception, there are 3 main possible approaches:

- Progestin: a prescription drug that induces anestrus, inhibits ovulation, and to a certain extent, interferes with spermatogenesis.
- Melatonin: 'off-label' implants that mimic the release of endogenous melatonin during short photoperiods causing suppression of sexual activity (anestrus) and has very limited effect on ovulation and spermatogenesis.
- GnRH agonist: disrupts reproductive functions in female and male. However, the only implant available (deslorelin – Suprelorin 4.7 mg® Virbac) is used 'off-label' in cats.

Another method is to induce ovulation and therefore pseudopregnancy resulting in lack of estrous signs due to high concentrations of progesterone for ~ 45 days. Ovulation is induced by hCG or mechanical vaginal stimulation and/or teaser male (vasectomized or even neutered tomcats).

Currently, different hormonal approaches (long-term implants of GnRH agonist, melatonin implant, and GnRH vaccine) are possible as alternatives to progestin. These preparations appear to exhibit adequate contraceptive effect with less unfavorable effects than progestins.

Progestins

Currently, progestins are the most used contraceptive agents to prevent estrus in the queen. The mechanism of contraception remains controversial and pathways (negative feedback and suppression of GnRH, interference with gamete transportation, and blockage of implantation) have been suggested. There are drugs with oral or injectable formulations. The oral formulation is known as the 'cat contraceptive pill.' The most widely used active substance is megestrol acetate (MA). However, there are also 2 other progestins, medroxyprogesterone and proligestone. The major limitations of progestins are the intensity and severity of side effects that vary in relation to the drug, dose, frequency and phase of the estrous cycle in which given and pre-existing medical conditions. Cases of mammary cancer, mammary hyperplasia, cystic endometrial hyperplasia/pyometra complex, ovarian cysts, and hormonal disorders like diabetes mellitus were observed in animals treated with progestins (reviewed[1]). Affinity of progestin to the progesterone receptor and to steroid hormone receptors (e.g. androgens) and/or glucocorticoids will also impact its side effects. However, the dose appears to overcome the affinity, as lower dosages of MA seem to guarantee a higher level of effectiveness while reducing the risk of side effects

to a minimum, both in frequency and in severity.[2] During the COVID-19 pandemic, due to the reduction in spaying program, MA became a good alternative.[3] Low doses of MA (0.625 - 0.1-0.2 mg/kg weekly), can be given safely; in practical terms, an oral dose of 2.5 mg of MA per female once a week is adequate. In case the queen has signs of estrus, the dose should be 5 mg per cat per day for 3 days, followed by once weekly treatment schedule. However, this protocol should be applied with care due to an increased risk of pyometra. In Italy,[2] a lower dose (0.01 - 0.03 mg/kg once a day) of MA (Estropill, MSD) is currently available, but needs further investigation. It is important to adhere to the duration of treatment (maximum of 2 weeks) to prevent the queen returning to cyclicity. Progestin treatment should not be extended beyond 2 years, ideally ≤ 1 year.

Melatonin

Suppression of estrus in female domestic cats by melatonin mimics the physiological events of seasonality observed in many animals (e.g. horse, sheep, and hamsters). During dark periods, the pineal gland secretes melatonin (N-acetyl-5-methoxytryptamine). In queen, melatonin suppresses hypothalamic secretion of GnRH, thereby this neuromodulator has an inhibitory effect on the female reproductive cyclicity.[4]

Melatonin is available as oral preparation, but the need to medicate cats every day limits this formulation. Our group used oral melatonin and the results were not very remarkable and the reluctance of the queen to ingest the tablet was a limitation.[5] Nevertheless, estrus was suppressed (~ 63 days) from the beginning of treatment when melatonin (4 mg tablets/cat/day [Melatol®, Elisium S.A., Buenos Aires, Argentina]) was given 2 hours prior to lights off.[6]

Currently, the best option is the melatonin implant (Melovin, Ceva, Marseille, France). Its use in domestic cats is 'off-label,' but it is still a good alternative to inhibit estrous behavior for short periods. The success rate is > 80% and the duration of suppression is variable. Suppression of estrus was observed on an average for 103.9 days (56 - 156 days) in 81.4% (22/27) of implanted queens (reviewed[7]). In a survey by our group,[8] prevention of estrus as reported by owners was 79% (33/42 queens). No side effects were reported in neither studies nor in clinical setting. The selection of queens is very important. Melatonin implants will have a better chance to induce anestrus in females having marked seasonality. Another aspect to improve the response is in choosing the best time of estrous cycle for implantation. If implanted during the early part of interestrous interval, longer suppression of estrus is observed. In practical terms, before using melatonin implants, the anamnesis will guide the likelihood of a positive response. It appears that some breeds are more susceptible to the photoperiod. Before implantation, progesterone concentrations should be measured (to avoid implanting females that had ovulated) and a vaginal smear done to evaluate whether the queen is in estrus. In case of an estrous smear, it is recommended to reexamine the queen 1 week later, if possible, to maximize the duration of suppression by implantation during interestrus. The effect of the melatonin implant is not instantaneous, some queens may have estrus up to 10 days postimplantation,[7,8] therefore treated animals should be separated from a tomcat for at least 2 weeks to avoid unwanted mating. Due to the lack of side effects and success of estrus prevention (up to 3 months), melatonin implant is a good option as a short-acting contraceptive for privately owned queens.

Deslorelin

GnRH agonist - deslorelin, is a slow-release implant (Suprelorin 4.7 mg, Virbac) that can be used to suppress estrus and to inhibit spermatogenesis in queens and tomcats, respectively. After a short interval of hyperstimulation ('flare-up' effect), both females and males have a downregulation phase of GnRH secretion and consequently have lower concentrations of FSH and LH. Side effects are not often observed, and in case of any undesirable effect, the implant can be removed. Reversible weight gain appears to be the main side effect reported in males and females.[8] The limitation is the duration of action. Although most of the studies had an efficacy on average for 13 (males) or 16 (females) - 22 months,[8,9] some animals may be suppressed for up to 3 years. Therefore, this choice for breeding animals should be made with caution. The only formulation used by our group is the 4.7 mg implant. The contraceptive effects are reversible with normal pregnancy rates and litter sizes with good maternal behavior.[8,9] In prepubertal queens, the implant allows the postponement of onset of puberty to an age close to 2 years.[10]

Implantation

The procedure by our group is to insert the implant (of deslorelin or melatonin) in an area posterior to the umbilicus (for ease of placement and removal if necessary). Rarely the animal (male or female) needs sedation, the cat is placed on dorsal recumbency with mild restraint. Local anesthesia (lidocaine 10%) is applied at the site of injection. Suprelorin® has an applicator and for the Melovin®, an applicator is adapted. The site of implantation is scrubbed and the implant is injected subcutaneously (SC). It is easy to verify the location of these implants (Melovin® is ± 3 mm and Suprelorin® is ±10 mm).

Induction of ovulation and pseudopregnancy for short-term suppression

Estrus in the queen can also been interrupted by inducing ovulation. As mentioned above, a particularity of domestic cats is that mechanical stimulation of sensory receptors of the skin of the perineal region, vulva, vagina, and cervix induces ovulation. During natural breeding, the penile spines are the source of stimulation, and the number of days in estrus and the frequency of mating are highly associated with the intensity and frequency of the LH surge[11] and thereby ovulation. Ovulation without fertilization induces a prolonged state of luteal activity and therefore absence of estrus known as pseudopregnancy. The duration of pseudopregnancy is variable from 35 to 76 days (average 45 days)[12] by a sterile tomcat, hormonal treatment or mechanical stimulation of the vagina.

Vaginal stimulation with a cotton swab can be used to mimic the stimulus caused by penile spines during copulation and therefore induce the LH surge. The procedure needs to be repeated to achieve the goal (induce ovulation). There are 2 limitations to this method of contraception. First, the technique is not always well tolerated by the female cat. Second, the use of the procedure repeatedly can increase the risk of pathologies related to progesterone exposure.

Immunocontraception

Immunocontraception is a subject of research and is still not available in the clinical setting. Although results of GnRH vaccine and zona pellucida vaccine have not been very successful in cats,[13-15] a study using a single-dose GnRH immunocontraceptive vaccine (GonaCon™) had promising results.[16] Limitations of immunocontraceptives are, the need of booster vaccinations to improve response, return to fertility once antibody concentrations decrease and severe lesions at the site of the injection due to adjuvants in the vaccines to improve efficacy.

General consideration

The best contraceptive choice depends on availability, safety, security and efficiency. The request for a contraceptive for domestic cats is a high demand amongst our clientele. Although progestin is not used frequently, we strongly believe that the adaptation of the dose and the selection of animals can substantially decrease side effects. Currently, for short duration of estrus suppression, the melatonin implant is normally chosen. The success rate is encouraging and some females have been repeatedly treated over more than 1 breeding season. For long-term suppression, deslorelin is a good tool for animals with conditions that preclude anesthesia. In case of breeding stock, as mentioned before, the lack of control over the duration of suppression should be extensively discussed with the owners to avoid disappointment and regrets due to the loss of animals for reproductive purposes. In some situations, it may be judicious to remove the implant after 4 months of implantation to reduce the duration of downregulation. Return of fertility has been well documented in both male and female cats. However, the quality of semen in some tomcats may not be enough to guarantee pregnancy after deslorelin implant. The age of animals at implantation is an important consideration. Selection of contraceptive for pet owned cats should always consider the breeding value of the animal, age, health, and duration of suppression. There is still a need for a more practical solution to control cat overpopulation than the current methods.

Conflict of interest

None to report.

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