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Review

Low-dose megestrol acetate revisited: A viable adjunct to surgical sterilization in free roaming cats?

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ABSTRACT

Approximately 2–3 million cats are euthanased in animal shelters across the United States annually. Preventing pregnancy in cats is a key step to reducing this number. While surgery is generally a safe and effective tool for curbing reproduction in cats, it is not a practical method to achieve the reduction in numbers required for an appreciable impact on the cat population as a whole. Low-dose megestrol acetate (MA) is a synthetic progestin that has been used for the management of reproduction in free roaming cat populations; however, there has been no regulatory oversight regarding the use of this product for this purpose. Additionally, there is a paucity of data regarding the safety and efficacy of the product for the management of reproduction in free roaming cats. The purpose of this review is: (1) to outline the need for a non-surgical contraceptive in cats; (2) to discuss the uses of MA in domestic cats; (3) to consider potential adverse effects of the drug, and (4) to discuss regulatory challenges associated with the use of MA in free roaming cat populations. In order to answer the questions posed in this review, more data will need to be collected in laboratory and field studies.

Introduction

Approximately 4 million cats enter animal shelters in the United States annually, and close to 70% of these are euthanased.[1] At least 47% of all US shelter feline intakes are kittens (New et al., 2000). Further, nearly 27 million kittens are born to owned cats in the US each year, with as many as 145 million born to free roaming cats (Levy, 2010). It is evident that euthanasia and deaths in the wild are the leading reasons for losses among domestic cats in North America.

In addition to animal welfare concerns precipitated by the euthanasia of large numbers of cats, the management of free roaming cat populations that are important sources of shelter admissions has public health implications. Cats have been shown to transmit rabies virus (Vaidya et al., 2010), as well as other infectious agents to humans (Kravetz and Federman, 2002). Additionally, there are concerns that free roaming cats can disrupt ecosystems and have potentially deleterious effects on wildlife (Medina et al., 2011). It seems clear that reducing the intrinsic reproductive rate in free roaming cat populations could ultimately lead to decreased feline intake in animal shelters, decreased euthanasia, reduced suffering for free roaming cats that never enter an animal shelter, and reduced disease and environmental concerns.

Currently, surgical sterilization is the only form of contraception that is commonly used to manage free roaming cat colonies. Spay/neuter surgery is expensive, invasive, labor-intensive, and can only be performed by veterinarians. Therefore, alternative forms of contraception have received more interest in recent years. Low-dose megestrol acetate (MA), a synthetic progestin, is an alternative to surgical sterilization that is used by some colony caretakers in the US to manage reproduction in specific free roaming cat populations. However, MA has never had a label claim for use in cats, and many questions about its safety and efficacy for feline contraception remain.

The purposes of this review are: (1) to outline and discuss the need for a non-surgical feline contraceptive; (2) to describe the historical and present use of MA to control reproduction in free roaming cats; (3) to describe side effects associated with MA, and (4) to consider potential regulatory pathways for the use of MA in free roaming cat populations.

The need for a non-surgical contraceptive

Free roaming cat populations typically are managed in one of three ways: (1) laissez-faire management involves simply doing

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[1] See: ASPCA, 2012. ASPCA Pet Statistics. http://www.aspca.org/about-us/faq/pet-statistics.aspx (accessed 28 January 2013).

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nothing – allowing the size of the population to vary without any human involvement; (2) trap-euthanase programs that comprise large-scale euthanasia of free roaming cats, and (3) trap-neuter-return (TNR) programs, which involve trapping cats (often in large numbers) and transporting them to a facility where sterilization surgery is performed (sometimes in conjunction with other services, such as vaccinations), then returning the cats to the colonies from which they came. Although by its very nature it is often not discussed, the laissez-faire approach is arguably the most common among the three.

While trap-euthanase programs were postulated in one population modeling study to be potentially more effective than TNR in reducing population sizes over time (Andersen et al., 2004), in practice, lethal control methods have only been shown to eradicate cats on small isolated islands with small cat populations where repopulation cannot occur from neighboring areas. Lethal methods and large scale trap and removal programs can result in rapid depopulation in the short term, but they soon prove unsuccessful because of repopulation through breeding and immigration (Slater, 2005; Robertson, 2008). However, other studies have shown TNR to be more effective, and potentially more sustainable over time with regard to attracting and keeping the volunteers needed to participate in and fund the programs (Levy and Crawford, 2004; Robertson, 2008; Loyd and Miller, 2010). The reasons for different study outcomes are complex and can be impossible to control for when designing studies to measure such effects.

Even if TNR programs are shown to be effective at reducing population sizes and are attractive to stakeholders in the community, such programs are not without flaws. Staff and/or volunteers often must trap a large number of cats over a short period of time. These cats are then housed in traps and must be transported to a surgical facility, all of which is stressful. High-quality, high-volume spay-neuter clinic models have increased efficiency and decreased costs, but the problem remains that costly infrastructure and trained staff/volunteers are necessary (Looney et al., 2008; White et al., 2010). In addition, unlike owned cats, free roaming cats usually do not have people who are invested in their welfare and willing to pay for the cost of surgery.

Even with the use of well-developed TNR clinic models, it is unlikely that surgery alone will ever be able to sterilize the number of animals required to achieve a real reduction in the intrinsic reproductive rate of free roaming cat population. Population modeling data suggest that the proportion of free roaming cats that must be sterilized in an 'average' such population, to effectively decrease the intrinsic reproductive rate, is very high – as many as 70% of reproductively active juveniles and even greater numbers of adults (Budke and Slater, 2009). Anecdotally, TNR program managers frequently report seeing litters born to females who have yet to be trapped and sterilized. The litters produced by these females can effectively counter the effects of surgical sterilization in the rest of the colony. TNR program managers and free roaming cat colony caretakers have long sought a method of feline population control which can be used where surgery is unavailable or inconvenient, or as an adjunctive intervention (to use 'while waiting' for surgery), reflecting the idea that TNR only is not likely to be a complete solution to free roaming cat reproduction. In addition, a demand for surgical alternatives exists among animal welfare groups and others interested in reduction of free roaming cat populations.

Since the introduction in 2008 of a large program dedicated to funding studies investigating non-surgical cat and dog sterilization,[2] significantly more research has commenced in this field. However, low-dose MA is currently the only widely available alternative to surgery for contraception in free roaming cats in the USA. Many questions remain regarding MA in relation to safety, efficacy, regulatory pathways and ethics.

Use of MA in cats

MA is a synthetic progestin. It is a tasteless, odorless powder (Plumb, 2005). Like other progestins, it is known to inhibit reproduction, although the exact mechanism of its action remains to be elucidated. Proposed mechanisms of action include: (1) altered motility of the reproductive tract; (2) altered receptivity to oocyte implantation, and (3) negative feedback on the hypothalamus and pituitary gland, leading to decreased release of gonadotropin releasing hormone (GnRH), follicle stimulating hormone (FSH), and luteinizing hormone (LH; Munson, 2006).

MA has not received Food and Drug Administration (FDA) approval for any specific use in the domestic cat in the US. Historically, MA has been used off-label at higher doses to address a variety of disorders in cats, including dermatological, behavioral, and reproductive conditions (Romatowski, 1989). The doses of MA used for these purposes have ranged from approximately 0.5–1 mg/kg, typically administered at daily or alternate-day intervals. Adverse events have been reported in association with MA administered at these dose rates, and US veterinarians have, in turn, been reluctant to use MA in recent years. There are minimal data regarding the use of MA to control cat reproduction. However, during one field trial in which 244 adult cats were given 2.5 mg weekly of MA for a minimum of 30 weeks, one cat developed pyometra, two previously pregnant animals had abnormal births, and 21 cats showed signs of estrus (Oen, 1977).

In the US, the use of MA as a free roaming cat contraceptive became more widespread when it began being marketed as FeralStat by a private veterinarian in Connecticut, USA.[3] The active ingredient in FeralStat was MA; it was mixed with a lactose powder to increase palatability and the package insert indicated weekly dosing at approximately 0.1–0.2 mg/kg MA. This dose was significantly lower than other commonly reported dosing regimens. FeralStat was administered to animals in managed colonies by mixing it with a palatable ('wet') cat food. The intention of this product was that it be used as an adjunct to surgical sterilization. Essentially, it was to be used to prevent pregnancies and litters in animals 'waiting' to be spayed as part of a TNR program. Some colony caretakers have used this product instead of surgical sterilization, but no data exist reflecting the numbers of colonies managed in this fashion. In addition, it should be noted that FeralStat typically was dosed to groups of free roaming cats by setting up several 'feeding stations,' leading to challenges regarding dosing accuracy.

As of autumn 2011, the FeralStat website was no longer functioning, and the company was no longer responding to inquiries. Although FeralStat is no longer marketed, a demand exists for such a product. Some free roaming cat colony managers, working with private veterinarians, have obtained a generic form of MA. It should be noted that current use of this product is occurring outside of any regulatory oversight. All current formulations are generic; there are no entities marketing MA for use in free roaming cats in the US, and the FDA has not approved this use of MA.

A number of questions about the use of MA in cats remain. For example, does a valid veterinary-client–patient relationship exist if veterinarians provide this product to free roaming cat colony caretakers? What are the limits of safety and efficacy? What are its environmental impacts? What effect do different dosage regimens

[2] See: Found Animals Foundation, 2011. Michelson Prize and Grants. http://michelson.foundanimals.org/michelson-prize (accessed 29 January 2013).

[3] See: Alliance for Contraception in Cats and Dogs, 2009. FeralStat product position paper. http://www.stray-afp.org/wp-content/uploads/2012/07/Feral-Stat-Product-Profile-and-Position-Papers.pdf (accessed 28 January 2013).