Surgery Not Required: Current and Future Options in Fertility Control of Dogs and Cats

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Introduction

The Pill, approved in the United States in 1960, was considered a breakthrough in contraception for women. Daily oral treatment with low dose estrogen or estrogen/progesterone combinations became a widely adopted method for human reproductive control. Research has been published for more than 40 years indicating that non-surgical contraception for animals is possible. Since daily treatment with steroids is impractical for most species, other methods have been explored. Across the globe, there is a tremendous need for new methods of sterilization that are faster, easier, and less expensive than surgery. Non-surgical fertility control can address this need.

History

A variety of approaches have been used in many species of animals, including early laboratory work in rodents and studies on dogs, cats, cows, and monkeys. Much of this work was directed towards exploring contraceptive approaches for humans, but some of it was clearly geared towards creating alternatives to surgery for animals. Over the years, technical issues and pitfalls have stood between various approaches and the marketplace. In addition, there are sociopolitical factors that have likely slowed the advance of contraception and fertility control in animals.

Contraceptive medications in dogs and cats have only had more recent attention in the latter half of the 20th century. Around 1960, due to the availability of orally active and increasingly more effective progestins ("The Pill"), efforts began on a larger scale to control reproduction in dogs and cats. As oral contraception products became widely available for women, the desire to use these products in pets became more mainstream. The status of dogs and cats also changed during this time to true companions, family members, and even child substitutes. It was at this time that animal welfare advocates began to be concerned about the fate of unwanted and unplanned offspring and the horror of increasing numbers of dogs and cats euthanized each year, and launched educational campaigns to inform the public about preventing unwanted litters. Progestin-based "Pills for pets" were developed in Europe, coming to the market in 1963. Large-scale population control for dogs and cats in the US began in the early 1970s.

Medroxyprogesterone acetate (MPA) in tablet form was the "Pill" that was marketed first in Europe in 1963. In the US, MPA was marketed as an injectable product and was used in dogs with disastrous results. Introduced in 1964, MPA was produced as a long-acting crystalline suspension (4-5 months duration, Promone-E® or Depo-Provera®). This product was very effective in estrous suppression but caused pronounced cystic endometrial hyperplasia in the uterus, resulting in an epidemic of pyometra.

Megestrol acetate (MGA) was another early progestin that was marketed for use in dogs in Europe, the US, and Canada, beginning in the early 1970s. This product is an oral tablet that has been the only product approved for use in the breeding bitch in the US. Marketed as Ovaban®, there were two protocols approved for use in the

dog. One was at a higher dose and short duration to stop a cycle once begun. The other protocol was at a lower dose and longer duration to prevent the cycle from occurring. Although the marketing of MGA as a specific veterinary product has been discontinued, MGA is available as a generic for human use but used only on a limited basis in the US.

The next hormonal approach to contraception in small animals to be developed was gonadotropin-releasing hormone (GnRH) analogs. The advantage to using GnRH or its analogs is that these compounds are effective in males and females, since GnRH is the master control hormone for reproduction. Also, the GnRH decapeptide has the same amino-acid sequence in all mammals, making any product potentially useful in a variety of species. One drawback is the high cost of these analogs. Peptech Animal Health in Australia developed two much less expensive implants for either a 6- or 12-month suppression of fertility in male dogs using the GnRH analog deslorelin. Research showed that treatments with these implants resulted in cycle control in the bitch and queen, and in suppression of spermatogenesis and libido in male dogs. Its use has been studied in male cats but the product is not approved for this use. Approval for the sale of the deslorelin implant for use in male dogs under the trade name Suprelorin® was obtained in New Zealand and Australia in 2003 and in the European Union (EU) in 2007.

Hormonal antigens are another avenue to immunocontraceptive vaccines. The antigenicity of GnRH complexes has been confirmed since the 1970s. Because small peptides make weak antigens, they must be conjugated to large proteins and potent but safe adjuvants are needed. In 2004, Pfizer Animal Health acquired the Australian animal health company CSL and its US subsidiary Biocor, which had a gonadotropin-releasing factor (GnRF, another term for GnRH) vaccine for use in male dogs for the treatment of benign prostatic hyperplasia. Although Pfizer obtained a conditional license for this product for treatment of canine BPH from the United States Department of Agriculture (USDA) in 2004, no further licensure occurred in the US and the product is no longer available. GonaCon™, a GnRH vaccine, has been developed by the National Wildlife Research Center (NWRC) of the USDA APHIS Wildlife Services (WS). After beginning initial research in 1991, NWRC began developing the single-shot, multiyear contraceptive for white-tailed deer in 2005. The vaccine received USDA licensure for use in white-tailed deer in 2010, and wild horses and burros in 2013. The GonaCon vaccine induces a long-lasting contraceptive response with a single injection; a single shot can successfully keep female mammals infertile for 1 to 4 years without boosting, and infertility is reversible over time as antibody levels decline.

Beginning several decades ago, efforts were undertaken to find a safe single intratesticular treatment causing the testes to atrophy. A variety of compounds have been tested. The first approved product (Neutersol®, zinc gluconate/arginine) to fulfill both the safety and effectiveness criteria required by the FDA became commercially available in the US in 2003. Distribution was halted in 2005 when the patentholder and marketing company severed ties. Neutersol is no longer available in the U.S; however the product has been brought back to certain markets re-named as Esterilsol®, sponsored by a company named Ark Sciences, Inc. The product is approved in several Latin American countries. In 2013, Ark Sciences brought the product back to the US under the new name, Zeuterin™. Unlike the GnRH treatment, which in most animals is reversible, intratesticular treatments result in irreversible destruction of germ cells and hormone-producing tissues.

Current and Potential Future Products

Zeuterin™ (zinc gluconate/arginine) is the only FDA-approved non-surgical sterilant available for companion animals in the US. It is labeled for use in male dogs from 3-10 months of age. An intratesticular injection causes permanent and irreversible sterility, and the requisite FDA study for product registration showed that testosterone levels of treated dogs were 41-52% lower than intact dogs. The product is available to licensed veterinarians who are trained in the Zeuterin™ injection technique. Zeuterin appeals to a demographic of clients who have concerns about surgery, or simply want their dogs to retain their testicles; it also has found a niche with a scattering of low-cost sterilization programs throughout the US.

Another intratesticular injection, calcium chloride, has been reported to cause permanent and irreversible sterility in male dogs when mixed with ethyl alcohol. The product is not approved by the FDA, and its use is considered experimental.

Suprelorin® (deslorelin) has been shown to provide effective long-term contraception in bitches and to effectively suppress ovarian activity in cats, but it has not been approved for contraceptive use beyond male dogs. It is approved in the US to treat adrenal disease in ferrets. Another noteworthy application is its current use (via experimental drug license) by Dr. Judith Samson-French and her team through the Dogs With No Names project, in which implants are applied to female dogs living on the First Nations Reserves in Canada.

As referenced above, the GnRH vaccine (GonaCon) induces a long-acting contraceptive response in a number of mammalian species. Efforts are underway to fully explore its contraceptive potential in free-roaming cats. A previous study demonstrated the safety and efficacy of GonaCon in female cats in a laboratory setting (Levy et al., 2011). Fifteen female cats were injected intramuscularly with 0.5 ml GonaCon vaccine, and 5 control cats were injected with 0.5 ml sham vaccine. A breeding trial, starting on study Day 120 post-vaccination, demonstrated that vaccinated cats had a longer time to conception (median 39.7 months) compared to sham-treated cats (4.4 mo; $P < 0.001$). A total of 93% of vaccinated cats remained infertile for the first year following vaccination, and 73%, 53%, and 40% were infertile for 2, 3, and 4 years, respectively. At study termination (5 years after a single GonaCon vaccine injection), four cats (27%) remained infertile. Serological testing showed GnRH antibody titers declined more rapidly in short-term responding cats with < 2 years of infertility (n = 4), compared to long-term responding cats that experienced fertility control for >2 years (n = 11) ($P < 0.05$). Given the promise of the laboratory study, a field study is now underway at the University of Illinois that will test the safety and efficacy of a similar GnRH-based vaccine under field-like conditions that simulate a free-roaming cat colony.

What the Future Holds

The Michelson Prize & Grants in Reproductive Biology is an undertaking of the Found Animals Foundation to incentivize research in reproductive biology and other fields, with the ultimate aim of developing a permanent, single-dose non-surgical sterilant for male and female cats and dogs. The Michelson Prize & Grants program has designated $50 million in grant funding and a $25 million prize to the researcher(s) who can develop a product that meets the program's criteria. This program has stimulated numerous research projects aimed at developing a suitable non-surgical sterilant for dogs and cats. Researchers are looking into a number of ways to permanently sterilize cats and dogs without surgery, including: (1) a vaccine that would block the release of sex hormones, (2) a virus that would genetically silence fertility pathways, (3) a chemical that would destroy eggs, (4) a targeted cytotoxin that would destroy cells necessary for the production of sperm and eggs, and (5) a vaccine that would block sperm from entering eggs.

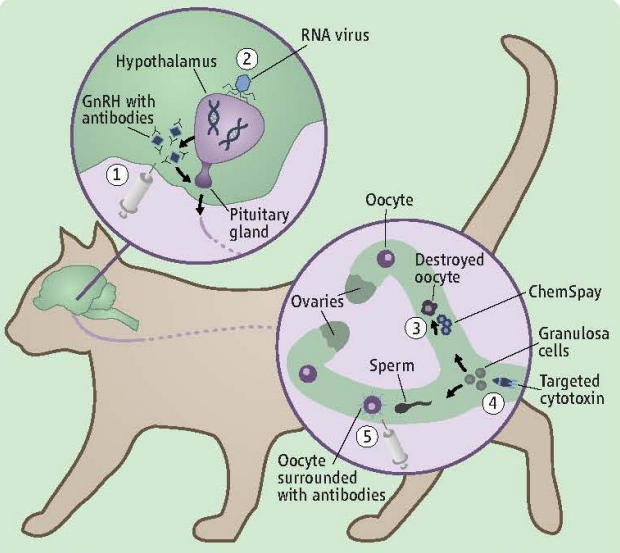

Figure 1. Sterilization strategies. Researchers are looking into a number of ways to permanently sterilize dogs and cats without surgery.

Conclusions

There is a long road from demonstrating that a certain contraceptive approach can suppress fertility in a dog or a cat, and achieving regulatory approval for a product that can be marketed. Although some approaches can be shown to be safe and effective, the time and technical expertise required for developing a manufacturing process that can be scaled up and result in a stable, reproducible product is often the main obstacle to regulatory approval. Regardless, the need exists for products to help with animal population control worldwide. As new tools are developed to prevent animal reproduction, countless lives will be spared in shelters and on the street.

References

Alliance for Contraception in Cats & Dogs. (2013). *Contraception and Fertility Control in Dogs and Cats*. Retrieved from http://www.acc-d.org/resource-library/e-book

Grimm D. *Science.* Vol. 325. 18 September 2009. 1490-1493. Retrieved from http://www.sciencemag.org on September 22, 2009

Levy J. *Current contraceptive approaches for feral cats*. Paper presented at: 4th International Symposium on Non-Surgical Methods of Pet Population Control; 2010; Dallas, TX.

Levy J. *A Look at Future Tools to Control Free-Roaming Cat Populations*. Paper presented at: 4th International Symposium on Non-Surgical Methods of Pet Population Control; 2010; Dallas, TX.

Levy, J.K., Friary, J.A., Miller, L.A., Tucker, S.J., & Fagerstone, K.A. (2011). Long-term fertility control in female cats with GonaCon™, a GnRH immunocontraceptive. Theriogenology, 76,1517–1525.