

REVIEW ARTICLE

NON-SURGICAL CONTRACEPTION IN MALE DOGS AND CATS

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Abstract. Orchiectomy results in irreversible sterility and may trigger a number of side effects such as underdevelopment of external genital organs, disturbances in the musculoskeletal system, obesity, increased risk of diabetes mellitus or hypothyroidism and behavioral problems. Therefore alternative methods of contraception have been developed during the last decades. This paper presents the clinical use of GnRH analogues with agonistic and antagonistic activity, chemical sterilization by intratesticular injections and the application of reproductive toxins, progestins and the possibilities of immunocontraception. The working mechanism, clinical results and possible side effects of these methods are discussed. The methods of non-surgical contraception, used adequately, are currently considered to be simple and effective.

Key words: dog, cat, male, non-surgical contraception

INTRODUCTION

Contraception serves to reduce the size of animal population and suppress physiological sexual activities. Furthermore it is carried out because of medical indications as well as behavioral problems. The most frequently mentioned

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undesirable male behaviors are aggression towards other males or people, roaming, fighting with other males, inappropriate sexual behavior (mounting of other animals or people), fear of inanimate stimuli and urine marking in the house [Maarschalkerweerd et al. 1997, Neilson et al. 1997]. The contraception also prevents sexually transmitted diseases, such as *Brucella canis* or canine transmissible venereal tumour (Sticker tumour). Furthermore contraception becomes more often a prerequisite for adoption of animals from shelters. Early sterilization of dogs and cats is frequently conducted, resulting in accelerated adoption procedures [Lieberman 1987, Stubbs and Bloomberg 1995]. When choosing a method of contraception one should be guided by the main objective for contraception – i.e. whether it should be a permanent or a temporary, reversible contraception. Among surgical methods the most widely used procedure is removal of the testes by castration (orchietomy, orchidectomy). This article however presents the non-surgical alternatives for contraception in male dogs and cats.

GnRH AGONISTS – SUBCUTANEOUS IMPLANTS

Gonadotropin-releasing hormone (GnRH) analogues have been of interest for a long time as preparations to control animal reproduction. More than 2000 preparations were developed and investigated during the last 3 to 4 decades [Padula 2005]. Agonists exhibit similar effects to the natural gonadoliberin – decapeptide secreted by the hypothalamus, but often have a much higher potency. They are used in biotechnology breeding programs and for the treatment of infertility. Paradoxically, when they act for a longer period, they inhibit the hypothalamic–pituitary–gonadal axis and may therefore be used as contraceptive agents. Due to the protein nature of these chemicals and their possible digestion in the gastrointestinal tract, the oral route is not advised; therefore they are administered parenterally. Attempts have been carried out to use different GnRH analogues, such as nafarelin by daily injections [Vickery et al. 1985] or leuprolide in a single subcutaneous injection of slow-release formulation [Inaba et al. 1996], which resulted in a decrease of testosterone concentration and a reduction of the number of fertile sperms. The use of the subcutaneous implants containing 6.6 mg buserelin resulted in a decrease in testosterone concentrations to baseline values within 15 days while maintaining this state for almost 8 months [Riesenbeck et al. 2002]. One of the most popular and currently used GnRH agonist is deslorelin. This compound is classified as a superagonist, with biological effects which are 100 times more potent than endogenous GnRH [Padula 2005]. When administered once, similarly to natural gonadoliberin, this drug directly stimulates the pituitary gonadotropin secretion, and indirectly the gonads. However, the continuous release provokes an inhibitory effect on the hypothalamic–pituitary axis. The

essence of this phenomenon is to reduce the amount of receptor proteins (down-regulation) in the pituitary gland, causing insensitivity of the gland to the stimulatory action of GnRH. Finally the gonadal activity is suppressed. Consequently the testosterone secretion as well as spermatogenesis are temporarily inhibited. Prolonged supply of the analogue may be achieved by the use of a subcutaneous implant containing 4.7 mg deslorelin. After a single application the testosterone concentration remains at a subthreshold level for at least 180 days; the lack of ability to fertilize lasts for about 9 weeks longer [Trigg et al. 2006]. One should note however, that the reproductive functions do not disappear immediately after inserting this implant. In one study complete sterility occurred on average 54 ± 21 days after the introduction of the implant, with variations from 40 to 84 days [Romagnoli et al. 2012]. On the market deslorelin is licensed as Suprelorin, a biodegradable subcutaneous implant for dogs; the same implant can be used for dogs with various body weights. The downregulation of the testicular function due to the slow-release of GnRH agonist resembles the processes observed in seasonally breeding animal species out of season [Hoffman and Goericke-Pesch 2014]. The prolonged action of deslorelin leads in all dogs to a reduction in the size of the testes and behavioral changes that occur from approximately 3 weeks after application of the implant. There is a complete disappearance of abnormal sexual behavior (mounting people and objects), improvement of the physical efficiency and a tendency for playing, increased appetite and a tendency, although ambiguous, for a reduced aggression towards other males. Behavioral changes are similar to those of castration [Morsink 2009]. In order to continue the contraceptive effect the administration of subsequent doses every 6 months is recommended. Only minimal side effects such as local skin irritation (slight edema), inflammation or hardening are observed after implant insertion. These minor side effect disappear spontaneously [EMA 2007]. In some regions of the world (e.g. Australia, several countries in Europe) another implant is available containing twice the amount of deslorelin (9.4 mg) causing a slower release of the active substance. The latter implants are administered at 12-month intervals [Morsink 2009]. One of the main disadvantages of 4.7 and 9.4 mg deslorelin implants however are the wide variation of action making it difficult to predict when the male dog will be fertile again. Indeed, several authors have shown that the down-regulation may be much longer than 6 or 12 months, respectively. In this respect, it is definitively advisable to discuss this long variation in action with the owners of valuable breeding dogs before the application of this compound.

The contraceptive implant Gonazon (18.5 mg azagly-nafarelin) is originally designed for females. However it displays its biological activity also in males. In one experiment performed in eight beagle males LH bioavailability decreased by approximately 70% during 11 weeks after Gonazon administration. After the ini-

tial increase lasting four days, the testosterone concentration dropped to baseline values within 3 weeks, and 2 to 4 weeks later all dogs showed aspermia [Ludwig et al. 2009]. Further studies were performed in a larger group of 53 dogs. A drop in testosterone concentration to subthreshold values ($< 0.35 \text{ nmol} \cdot \text{L}^{-1}$) occurred in all but two dogs and lasted for 6 to over 22 months. Starting from eight weeks after application a decrease in the size of testicles and prostate by 54 and 52%, respectively was observed. This effect on the prostate was more pronounced in dogs suffering from benign prostatic hyperplasia. There was also a significant improvement in cases of aggression [Goericke-Pesch et al. 2010].

The effectiveness of deslorelin implants was also investigated in cats. Administration of a 4.7 mg deslorelin implant resulted in a decrease of testosterone concentration, testicular atrophy and a decrease of spermatogenesis, as demonstrated in the ejaculated semen. The keratinized spines of the glans penis, which are indicators for the presence of testosterone in cats, disappeared within nine weeks. An increase in appetite and a marked decline in libido, copulatory behavior and urine marking was additionally noticed. During this period no side effects were observed [Goericke-Pesch et al. 2011, Novotny et al. 2012]. Subsequent studies have shown that in some individuals, despite the histological atrophy of testicular parenchyma, elongated spermatids were found, which may raise some doubts as to their complete infertility. In turn, pituitary desensibilization has been confirmed. Stimulation tests with buserelin (Receptal, 25 μg administered intravenously) gave a negative result, manifested by the lack of increase in serum testosterone concentrations [Goericke-Pesch et al. 2013]. One of the most important features of GnRH analogues is the reversibility of their effects, and return of reproductive function after the cessation of the implant's activity [Kutzler and Wood 2006, Trigg et al. 2006, Ludwig et al. 2009, Novotny et al. 2012, Romagnoli et al. 2012]. The current commercially available GnRH implants are summarized in Table 1.

GnRH ANTAGONISTS

GnRH analogues of antagonistic activity bind to GnRH receptors (without activating them) and thereby block the biological function of endogenous gonadoliberein. Therefore, they can also be used as contraceptive agents. Unlike GnRH agonists, they don't show an initial stimulatory effect. Some of these formulations result in significant bursts of histamine, which limits their practical use. However, more recently developed analogues do not show such a side effect, but the high costs restrict their wide application. Acyline is a third generation GnRH antagonist with the chemical structure of a decapeptide. In males the drug causes a partial decrease in libido, a moderate decrease in the size of the scrotal sac, and the deterioration of semen parameters. Additionally this leads to a decrease in the secre-

Table 1. Commercially available subcutaneous GnRH implants

Tabela 1. Komercyjnie dostępne implanty podskórne z GnRH

Trade name Nazwa firmowa	GnRH analogue Analog GnRH	Dosage Dawka	Duration of contraceptive effect Długość działania antykoncepcyjnego	Remarks Uwagi
Suprelorin	deslorelin	4.7 mg	6 months/dog, cat 6 miesięcy/pies, kot (2 years/ferret) (2 lata/fretka)	
		9.4 mg	12 months/dog, cat 12 miesięcy/pies, kot (4 years/ferret) (4 lata/fretka)	
Gonazon	azagly-nafarelin	18.5 mg	1–2 years 1–2 lata	
Ovuplant	deslorelin	2.1 mg	?	Designed for ovulation induction in mares; effective in estrus induction in bitches Przeznaczony do indukcji owulacji u klaczy; skuteczny w wywoływaniu rui u suk
Zoladex	goserelin	3.6 mg	?	Used in humans for the treatment of prostate cancer and breast cancer Używany u ludzi do leczenia raka stercza i raka piersi
		10.8 mg		

tion of gonadotropins and testosterone, but after a single subcutaneous injection at a dose of $330 \mu\text{g} \cdot \text{kg}^{-1}$, these effects are short. No side effects were noticed [Gobello 2007, García Romero et al. 2009]. Similarly, in cats, a single acyline injection causes a transient disorder in spermatocytogenesis, spermiogenesis and deterioration of sperm motility [García Romero et al. 2012].

CHEMICAL STERILIZATION

This form of contraception is based on bilateral intratesticular injections of chemical preparations, ultimately leading to pathological changes in the gonads and permanent infertility. This method is technically relatively simple and inexpensive and is mainly intended for use in areas with large numbers of stray animals [Kutzler and Wood 2006]. This method was originally developed in North and South America. Different chemical compounds, such as saline solutions, formalin, or chlorhexidine in DMSO were investigated. However, zinc gluconate has been shown to be the most effective and is currently frequently used in commercial products manufactured under different names (Neutersol, EsterilSol, Zeuterin, Infertile, Testoblock). The drug is inserted through the disinfected skin of the scro-

tum. The administration does not require general anesthesia. Sometimes pharmacological sedation may be indicated, which allows for the exact placement of the drug. The volume of the preparation is adapted to the size of the testes. It can be used in puppies as well as in adult animals. Possible side effects are local pain or ulceration of the tissues, especially after inaccurate administration. A significant reduction in testicular size is not noticed [Cathey and Memon 2010, Oliveira et al. 2012]. Sometimes vomiting, lack of appetite, lethargy and diarrhea are observed. In dogs, two months after administration of the drug (0.2 to 1.0 ml per testis) azoospermia or oligospermia were observed. Blood testosterone concentrations decreased only slightly, and no significant influence on the libido was documented [Oliveira et al. 2012]. After intratesticular application in cats, the majority of animals (73%) displayed azoospermia. Moreover, reduction or disappearance of spines of the glans penis was observed. There was also a clear reduction in sexual behavior without a significant decrease in serum testosterone concentration in cats [Oliveira et al. 2013]. It is therefore assumed that this type of procedure causes permanent infertility, not eliminating the gonads as an active endocrine gland.

REPRODUCTIVE TOXINS

These compounds are defined as substances causing structural and functional disorders which impair fertility. The primary problem of these toxins is however the possible threat to people who have contact with these compounds in laboratories or in the industry. Toxins selected as contraceptives for animals conjugated to GnRH can disrupt the hypothalamic–pituitary–gonadal axis. Endogenous gonadoliberin binds to specific receptors in the pituitary gland, stimulating the secretion of gonadotropins. When a GnRH analogue conjugated to a cytotoxic substance is introduced into the body, this complex damages receptors, which may be used in the therapy of patients suffering from neoplasms possessing GnRH receptors [Paalyi et al. 1999]. The block of gonadotropin secretion may also play a role in the contraception. Pokeweed antiviral protein (PAP) originating from a plant of the genus *Phytolaccaceae* was already tested. Conjugated GnRH–PAP was injected to adult dogs for 3 days. This toxin caused a decline in LH secretion, a decrease in testosterone concentration and a reduction in testicular size for about 5 months [Sabeur et al. 2003]. Similar results were obtained in dogs around puberty, at the age of 16–32 weeks [Ball et al. 2006].

PROGESTINS

Synthetic analogues of progesterone are widely used for contraception in female dogs and cats. However also in males attempts have been made to use these

preparations with various effects. Administration of medroxyprogesterone acetate at a dosage of $20 \text{ mg} \cdot \text{kg}^{-1}$ resulted in deterioration of semen quality in dogs, probably by direct effect on the epididymis. A better result was achieved using this progestin combined with testosterone esters [England 1997]. Progestins in oral, injectable or subcutaneous forms were also used for the treatment of benign prostatic hyperplasia, causing a temporary reduction of the gland [Jurka and Max 2006]. Drugs of this group appear to be quite effective in the treatment of unwanted sexual behavior in male dogs and cats. Improvement was achieved for several forms of aggression, urine marking, copulatory behavior and roaming [Max and Grabiec 2000]. However, one should note that long-term administration of progestins is associated with several side effects such as hyperglycemia, adrenal insufficiency, hepatitis, mastopathy and acromegaly [Max and Jurka 2006] and should therefore not be recommended. When the side effects appear the treatment should be discontinued. If long-acting formulations were used its residues should be removed. It is therefore recommended to mark the injection site, e.g. as tattoo, prior to the application [Max and Grabiec 2000].

IMMUNOCONTRACEPTION

It is known that immune processes play an important role in reproduction. On one hand, there are physiological mechanisms of immune protection of the gametes and embryos; on the other hand in pathological situations it may come to reproductive disorders such as immunological infertility [Max 1991, Max 2008]. There have been several attempts to utilize these phenomena for contraceptive purposes in dogs and cats. The method involves immunizing the body with antigens of proteins (usually in combination with an adjuvant) which are crucial for reproduction. Finally the production of antibodies are induced which will finally block the biological functions. The final aim is to obtain an effective contraceptive vaccine. A synthetic analogue of GnRH called GonaCon (primarily designed for free-living animals) is currently available. Its contraceptive activity is based on the formation of anti-GnRH antibodies. Administration of the vaccine in dogs causes a drop in testosterone concentration, sperm count and sperm motility. After a single injection the effects last for approximately a year. However due to the limited number of dogs included in these studies far-reaching conclusions should not be made. Vaccine administration may cause a transient local pain and slight swelling [Vargas-Pino et al. 2013]. A one-time injection of recombinant analogue of GnRH in cats aged 8–9 weeks resulted in formation of antibodies neutralizing gonadoliberin, which persisted for at least 20 months and was accompanied by cessation of the reproductive functions [Robbins et al. 2004]. In another study cats were immunized with GonaCon, which induced in the majority of animals a 6-month

contraceptive effect with an expression of a high titer of anti-GnRH antibodies ($> 1:32\ 000$), suppression of testosterone secretion, cessation of spermatogenesis and testicular atrophy [Levy et al. 2004]. Painless granulomas at the injection site were observed [Levy et al. 2011]. Another drug is Canine Gonadotropin Releasing Factor Immunotherapeutic (Pfizer) for the treatment of benign prostatic hyperplasia in dogs [Donovan 2013], existing on the American market since 2004. Two subcutaneous injections four weeks apart resulted in the production of specific antibodies lasting approximately 5 months and leading to a decrease in testosterone concentrations and testicular size. These results give rise to the possible use of these drugs for contraceptive purposes [Donovan et al. 2012]. Investigations are currently undertaken to develop contraceptive vaccines, using GnRH analogues conjugated with various antigens for the treatment of prostate cancer [Finstad et al. 2004, Walker et al. 2007, Junco et al. 2008]. These experiments are mainly conducted in animal models in order to potentially use these drugs in human medicine.

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NIECHIRURGICZNA ANTYKONCEPCJA U SAMCÓW PSÓW I KOTÓW

Streszczenie. Orchiektomia prowadzi do trwałej niepłodności, a czasem powoduje różne skutki uboczne, takie jak niedorozwój zewnętrznych narządów płciowych, zaburzenia w układzie mięśniowo-szkieletowym, otyłość, zwiększone ryzyko cukrzycy lub niedoczynności tarczycy i problemy behawioralne. Z tych powodów rozwijają się alternatywne metody antykoncepcji. Artykuł przedstawia zastosowanie analogów GnRH, zarówno o działaniu agonistycznym, jak i antagonistycznym, chemiczną sterylizację przez iniekcje dojadrowe oraz użycie toksyn reprodukcyjnych i progestagenów. Przybliżono także możliwości wykorzystania antykoncepcji immunologicznej. Omówiono zostały efekty kliniczne oraz skutki uboczne po podaniu poszczególnych preparatów. Metody niechirurgicznej antykoncepcji, właściwie zastosowane, uważane są obecnie za proste i skuteczne.

Słowa kluczowe: pies, kot, samiec, niechirurgiczna antykoncepcja

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