

<https://doi.org/10.31533/pubvet.v15n03a762.1-7>

Chemical castration of small animals: Where are we?

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Abstract The great number of stray animals in Brazil and around the world is considered a public health issue due to the potential zoonotic disease transmission. As a solution, population control based on cost-effective, non-surgical methods of sterilisation without postoperative complications are explored. The goal of this review is to show the most used chemosterilants, illustrating their commercial availability. In male animals, several studies proved that permanent sterility involving the use of calcium chloride or zinc gluconate can be achieved. Also, these chemosterilants may be potentialized and side effects reduced depending on which diluent is chosen. In contrast, the studies in female animals are rare. The chemical method needs to be better divulged and to be applied in practice, while there is a need of further progress to its application in females.

Keywords: Cats, chemosterilants, dogs

Castração química em pequenos animais: Onde estamos?

Resumo. O crescente número de animais errantes no Brasil e no mundo é considerado um grave problema de saúde pública devido ao potencial de transmissão de doenças zoonóticas. Como solução a essa problemática, o controle populacional que envolva métodos não-cirúrgicos de esterilização, que sejam, efetivos, economicamente viáveis e sem complicações pós-operatórias são cada vez mais buscados. O objetivo desta revisão é de mostrar o avanço sobre o tema castração química, salientando os agentes mais estudados, bem como ilustrar a disponibilidade comercial de tais métodos. Em machos, a maioria dos estudos que comprovam esterilidade permanente envolve o uso de cloreto de cálcio ou gluconato de zinco, com adjuvantes que podem potencializar o efeito esterilizante e/ou diminuir efeitos colaterais. Em contrapartida, ainda raros são os estudos encontrados em fêmeas. O método químico precisa ser melhor divulgado e utilizado na prática, enquanto ainda há necessidade de mais avanços para sua aplicação nas fêmeas.

Palavras chave: Cães, gatos, quimioesterilizantes

Castración química de pequeños animales: ¿Dónde estamos?

Resumen. El creciente número de animales callejeros en Brasil y en todo el mundo se considera un grave problema de salud pública debido al potencial de transmisión de enfermedades zoonóticas. Como solución a este problema, se busca cada vez más el control de la población con métodos no quirúrgicos de esterilización, que sean efectivos, económicamente viables y sin complicaciones postoperatorias. El propósito de esta revisión es mostrar el progreso en el tema de la castración química, destacando los agentes más estudiados, así como ilustrar la disponibilidad comercial de dichos métodos. En machos, la mayoría de los estudios que prueban la esterilidad permanente implican el uso de cloruro de calcio o gluconato de zinc, con adyuvantes que pueden mejorar el efecto esterilizante y / o reducir los efectos secundarios. Por otro lado, los estudios encontrados

en hembras todavía son raros. El método químico debe ser mejor divulgado y utilizado en la práctica, mientras que todavía se necesitan más avances para su aplicación en las hembras.

Palabras clave: Gatos, perros, quimioesterilizadores

Introduction

Overpopulation of stray animals consists of an alarming scenery, mainly in underdeveloped countries (Jana & Samanta, 2007). In Brazil, these animal populations are estimated over thirty million, around ten million cats and twenty million dogs (WHO, 2003). The negative impact on public health is related to zoonotic diseases proliferation/transmission (OIE, 2014), such as rabies (Gupta & Gupta, 2019), leishmaniasis (WHO, 2010) and Chagas' disease (Coura, 2015).

Massive castration of stray animals is considered the main alternative to reduce overpopulation, minimizing public health issues (Okwee-Acai et al., 2013). To this end, ovariohysterectomy and orchiectomy are the conventional methods applied for this purpose. However, both techniques have disadvantages for large scale application: high costs, time consuming, need of postoperative care, adequate location and veterinary staff (Adin, 2011).

As an alternative, different methods have been studied to lead sterility, among them, the chemical castration. The main advantages of chemical castration are the low cost and the possibility of massive use, encouraging public health organizations and governments to participate even with limited resources (Garde et al., 2016). There are different ways to use the chemical sterilization in animals: hormonal methods, immunocontraception and inorganic chemosterilants (Jana & Samanta, 2011; Seid & Terefe, 2019). This review will focus on the use of inorganic chemosterilants, considered permanent irreversible methods, and that also present lower costs (Jana & Samanta, 2011). The castration with inorganic chemosterilants is obtained by intradecidual injection, which promotes local inflammatory reactions and lipid peroxidation. As a result, irreversible gametes degeneration occurs leading to infertility (Oliveira et al., 2013). Intratesticular or intraepidermal injection are easier to perform than intraovarian application, so most of the studies about chemosterilants efficiency were performed in males.

Inorganic chemosterilants

The ideal inorganic chemosterilants should show irreversible capacity of halting gametogenesis and libido, be safe considering systemic toxicity and/or graves side effects, be accessible for large scale use (Wiebe & Barr, 1984) and achieve sterility in a single application (Jana & Samanta, 2007).

Seeking to obtain all these advantages, the ideal chemosterilant has been the subject of studies for more than five decades (Freund et al., 1953). Several agents have already been evaluated, highlighting dexamethasone (Dixit, 1979), formalin, chlorhexidine gluconate, dimethylsulfoxide (Pineda et al., 1977), cadmium chloride (Lymberopoulos et al., 2000), sodium chloride (Canpolat et al., 2016), monosodium glutamate (Mondal et al., 2018) and cypermethrin (Wang et al., 2019). Despite the testing of several chemical agents, two stand out due to the number of studies conducted and to the existence of commercial formulations: calcium chloride dihydrate (CaCl₂) (Leoci et al., 2019) and zinc gluconate (DiGangi et al., 2017).

Zinc gluconate

This agent was first developed to castrate male animals (Seid & Terefe, 2019), being described for the first time by Fahim et al. (1993). Several studies prove that zinc gluconate leads to irreversible fibrosis of the seminiferous tubules, testis network and epididymis, thus resulting in permanent sterilization after 30 days of application (Garde et al., 2016). However, its action does not reach Leydig cells, so the compound stops spermatogenesis, but circulating testosterone levels remain normal (Levy et al., 2008; Rafatmah et al., 2019). In cats, zinc gluconate was able to promote azoospermia 120 days after intratesticular application and caused even greater damage to seminiferous tubules than in dogs (Fagundes et al., 2014).

Due to the anatomic differences of felines' testicles compared to canines, after chemosterilant application, cats showed minimum sign of discomfort, which occurs at low frequency and only three hours after injection (Fagundes et al., 2014; Kutzler, 2015; Oliveira et al., 2013). In dogs, in ten thousand case studies, few animals presented discomfort, classified as moderate two days after application (Levy et al., 2008). More recent studies observed similar results (DiGangi et al., 2017).

In order to guarantee the viability of zinc gluconate as a chemosterilant, reducing those side effects and enhancing its sterilizing effect, several diluents have been tested. Dimethylsulfoxide (DMSO) was used as a vehicle because the hydroxyl radicals contribute to the biological activity and solubility of the zinc gluconate (Araujo-Lima et al., 2017). Also, the association of DMSO and zinc gluconate in intratesticular injections led to infertility within 15 days in dogs. This association showed no behavioral changes, thus proving to be safe and effective (Soto et al., 2009; Vannucchi et al., 2015).

Zinc gluconate neutralized with arginine is commercially available in USA (Zeuterin®) for use in male dogs aged three to ten months. It is believed that there is a wide market for various formulations based on zinc gluconate around the world. The drug's production based on zinc gluconate in Brazil (Infertile®), whose sterilants properties won regulatory approval a time ago (Massei & Miller, 2013) and has been applied by Brazilian veterinarians to promote sterility. Others Latin American countries, such as Mexico, Colombia, Bolivia and Panama, product (V) based on zinc gluconate is been used in cats and dogs. The cost of those products is estimated in US\$15 per dog, standard sized (ACC & D Publication, 2013). So, it brings discussion about the costs of a large-scale use of this chemosterilant in underdeveloped countries.

Calcium chloride (CaCl₂)

Another inorganic chemosterilant applied in large-scale is the calcium chloride (Seid & Terefe, 2019). CaCl₂ is a sterilant applicable in several species: dogs, cats, rodents and cattle (Massei & Miller, 2013). Different concentrations and doses have already been tested and established (Jana & Samanta, 2011; Leoci et al., 2014; Soumendra & Das, 2017), proving its effectiveness.

The CaCl₂ leads to complete necrosis, fibrosis and germ cells absence in testicular tissue (Jana & Samanta, 2011). Its mechanism of action is dose dependent, so the 20% concentration was more efficient. At this concentration, no alterations on levels of cortisol, glucose, urea, nitrogen and serum protein were noticed (Jana & Samanta, 2011). Moreover, 20% CaCl₂ was able to decrease testosterone serum (Soumendra & Das, 2017).

Another study used a single dose of intratesticular injection of CaCl₂ diluted in 95% ethanol in dogs, at 1mg/kg dose by weight body. Showing encouraging results, sterility was noticed after fourth week post injection and it became a viable alternative to surgical castration (Abu-Ahmed & Howaida, 2015). Besides the referral dose that uses body's weight, the volume of this chemosterilant can also be determined using testicular measurements in dogs, making the chemocastration more practical to be used (Leoci et al., 2014).

As ethanol also has sterilising properties when injected in testicles, its association with CaCl₂ was studied, in order to get a more efficient chemosterilant. Leoci et al. (2014) evaluated the association of 95% ethanol with CaCl₂ 20% to do chemical castration in 52 healthy dogs. That approach reduced the sexual behavior of the dogs, led azoospermia in 60 days and dog's welfare was guaranteed in the parameters assessed. Other procedures were also studied with CaCl₂ in order to improve its effects, such as DMSO (Paranzini et al., 2018).

In Brazil, the combination of CaCl₂ and DMSO was tested in different species, including canines and felines. Clinical evaluation, serum testosterone dosage and histopathological evaluation after orchietomy showed good results in cats, that were azoospermia and no penile spicules were seen. In dogs however, results showed that one in six maintained sperm production, testosterone measurements showed individual variation (Paranzini et al., 2018; Silva et al., 2018).

The use of intratesticular injection of CaCl₂, with different vehicles, has been studied and much progress has been made in getting a safer and cheaper method to induce the sterility in male animals (Paranzini et al., 2018). As a long term alternative and more viable than surgical castration, studies

conducted in underdeveloped countries report the importance of calcium chloride intratesticular injection, as in cats as in dogs (Jana & Samanta, 2011).

Chemosterilization in female animals

Although studies of non-surgical castration methods are well established for male animals, there is still a lack of similar studies in females (Cavalieri, 2017). The American Medicine Veterinary Association policy AVMA (2005) warned about the overpopulation of female cats and dogs in american continent. This concern data reflected in AVMA'S encouraging efforts to the development of non-surgical sterilization also for female animals.

Cavalieri & Hayes (2017) noted ovaries' intraabdominal location as a huge challenge to administration of chemosterilants. Patra & Bose (1990) evaluated an approach of cadmium chloride intraovarian injection by laparotomy to realize mass sterilization in adult bitches. At the time, this procedure was pointed as a solution to the issue of animal overpopulation in India (WFA, 2005). However, the use of this agent was considered unfeasible because it is a cancerigen substance (Ewere et al., 2017). Thus, once laparotomy access is done, the ovariectomy may be easily performed, becoming chemical castration a contradictory procedure.

Actually, studies of effects and dosages of chemosterilants in females are sparse. Only one article was found referring to intraovarian application of zinc gluconate, by laparotomy in five bitches. The animals were evaluated by ultrasound for 60 days and it was possible to verify the reduction on the ovary's measures. After this period, the ovaries were surgically removed and evaluated by histopathological exam. Follicular atresia and absence of corpus luteum were noticed (Mogheiseh et al., 2017) but the need of surgical assessment discouraged further use in ovaries. A research with long term follow-up and with large amounts of animals and that focus on a minimally invasive technique to reach the ovaries is still lacking for pets.

As a less invasive alternative to the surgical castration, Cavalieri, (2017) referred to the use of transvaginal ultrasound guided injection to administration of chemosterilant on cows' ovaries. Comparisons using saline solution, CaCl₂ 20% diluted in 95% ethanol and zinc gluconate neutralized by arginine were made in *Bos indicus* heifers. The results were promising, with reduction of the ovarian mass of heifers treated with CaCl₂ 20%, besides the absence of clinical signs of pain. However, no sterilization was seen in most animals. The authors indicate that doses/concentrations and volumes to be injected must be standardized. Also authors mentioned that new techniques whose avoid the chemosterilant reflux at the time of intraovarian injection are necessary (Cavalieri & Hayes, 2017). No similar studies were found in female pets.

Conclusion

The use of chemical sterilisation is conquering space on a global level. A large database confirms it is a safe and low-cost procedure for application in males' pets. Although many alternatives of chemosterilants that are available for both sexes are still not available. To turn chemical castration into an effective method of overpopulation control, studies in females must be stimulated.

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Recebido: 10 de fevereiro de 2020.

Aprovado: 16 de março de 2020.

Disponível online: 11 de janeiro de 2021.

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