Ciências Agrárias
SEMINA

DOI: 10.5433/1679-0359.2023v44n3p1059

Macroscopic changes in the mammary glands of healthy cats after progestogen administration

Alterações macroscópicas nas glândulas mamárias de gatas hígidas após administração de progestágeno

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Highlights

Administration of contraceptives in queens leads to various mammary changes.
There are few experimental studies on the administration of contraceptives to queens.
Mammary enlargement occurred in queens after experimental dose of contraceptives.

Abstract

The administration of contraceptives in female cats leads to problems such as pyometra, fetal maceration, mammary hyperplasia, and mammary neoplasms. Among the diseases caused by contraceptives, mammary hyperplasia has only been diagnosed in felines. However, few experimental studies have shown that contraceptive administration can cause feline mammary hyperplasia. This study aimed to evaluate the effects of the administration of a single dose of contraceptives in the mammary glands of healthy cats. Twenty cat owners who had administered contraceptives to female cats were selected. Animals were divided into two groups. Contraceptives were administered to cats in the first group, and saline solution was administered to cats in the other group (control). Before drug administration, all cats were clinically examined. Anamnesis, physical examination, blood count, biochemical tests, and abdominal ultrasonography were performed. Thirty days after the administration of contraceptives, all cats were examined, and the examinations were repeated. At 30 days, no changes were observed in the blood count or ultrasound findings. However, upon physical examination, all cats that received contraceptives showed generalized enlargement of their mammary glands. Cats in the control group

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Received: June 05, 2023 Approved: Aug. 08, 2023

were clinically normal. Ninety days after the procedure, the cats underwent an ovariohysterectomy. At that time, all cats were clinically normal and mammary enlargement regressed. It was concluded that a single contraceptive application could cause macroscopic mammary changes suggestive of hyperplasia in ten cats.
Key words: Feline. Mammary glands. Progestins.

Resumo

A administração de anticoncepcionais em gatas causa problemas como piometra, maceração fetal, hiperplasia mamária e neoplasias mamárias. Dentre as doenças causadas por anticoncepcionais, a hiperplasia mamária tem sido diagnosticada apenas em felinas. No entanto, poucos estudos experimentais comprovaram que a hiperplasia mamária felina pode ser causada pela administração de anticoncepcionais. O objetivo deste estudo foi avaliar os efeitos da administração de dose única de anticoncepcional nas glândulas mamárias de gatas saudáveis. Foram selecionados 20 tutores de gatos que administrariam contraceptivos em suas gatas. Os animais foram divididos em dois grupos. Anticoncepcionais foram administrados às gatas do primeiro grupo, e solução salina foi administrada às gatas do outro grupo (controle). Antes da administração do fármaco, todas as gatas foram examinadas clinicamente. Foram realizados anamnese, exame físico, hemograma, exames bioquímicos e ultrassonografia abdominal. Trinta dias após a administração dos anticoncepcionais, todas as gatas foram examinadas e os exames repetidos. Aos 30 dias, não foram observadas alterações no hemograma ou ultrassonografia. No entanto, ao exame físico, todas as gatas que receberam anticoncepcionais apresentaram aumento generalizado das glândulas mamárias. As gatas do grupo controle estavam clinicamente normais. Noventa dias após o procedimento, as gatas foram submetidas à ovariohisterectomia. Na ocasião do procedimento cirúrgico, todas as gatas apresentavam-se clinicamente normais, havendo regressão do aumento de volume mamário. Concluiu-se que uma única aplicação de anticoncepcional foi capaz de causar alterações mamárias macroscópicas sugestivas de hiperplasia em dez gatas.
Palavras-chave: Felino. Glândulas mamárias. Progestágenos.

Introduction

In female cats, the administration of contraceptives leads to several mammary pathological changes, such as hyperplasia, pyometra, abortions, and fetal death (Araújo et al., 2014).

Although the cause of feline mammary hyperplasia (MH) is unknown, evidence suggests that MH is a hormone-dependent lesion associated with the action of natural or synthetic progestational substances (Romagnoli, 2015).

Although commonly diagnosed, few experimental studies have shown that feline MH can be caused by contraceptive administration. Case reports and retrospective studies have described illnesses caused by contraceptives in female cats (Araújo et al., 2014; Oliveira et al., 2014).

In the presence of MH, epithelial and mesenchymal tissues of the mammary glands have higher proliferative activity than normal mammary tissues (Melo et al., 2021). In addition, proliferation of progesterone and growth hormone (GH) receptors has

been detected in the mammary gland cells of cats affected by MH (Pereira et al., 2004). The mammary glands are an extra-pituitary source of GH. This hormone releases insulin-like growth factors that are active mitogens commonly expressed in mammary fibroblasts (Mol et al., 1996). Because progesterone induces the release of GH, MH pathogenesis may be related to the synergism between progesterone, GH, and insulin-like growth factors in mammary tissues (Loretti et al., 2005).

Mammary neoplasms are the third most common type of neoplasm in female cats. However, the incidence is significantly influenced by sex, age, breed, ovarian status, and the use of progestin-based contraceptives. Thus, it is important to highlight that mammary neoplasms are often associated with contraceptive administration in queens (Dyulger et al., 2020).

Therefore, the objective of this study was to evaluate the effects of systemic contraceptive administration in a single dose on the mammary glands of healthy cats.

Material and Methods

Twenty owners who would administer contraceptives to female cats were selected from the clients of 10 companies that sold contraceptives for feline and canine females in the city of Umuarama (PR, Brazil). All owners purchased contraceptives and were approached by Veterinary Medicine students for inclusion in the project after completing the purchase. After agreeing to participate, the owners were instructed not to administer contraceptives or to take the female cats for examination. The owners were instructed to clinically examine the cats at a Teaching Veterinary Hospital on the scheduled date on which the contraceptive was purchased.

Before contraceptive administration, all cats were examined clinically. An anamnesis, physical examination, blood count, biochemical tests (alanine aminotransferase, creatinine, and urea levels), and abdominal ultrasonography were performed. Only cats that showed no changes during any of the examinations were included. It is important to select healthy females to avoid bias because some diseases can cause mammary changes in cats. Once selected, cats were randomly divided into two groups with the same number of components.

In the first group (AG), cats were administered contraceptives acquired by their owners (anticion and inibidex). All drugs were injectable and were administered subcutaneously in the right lateral abdominal region. Drugs were administered in accordance with the manufacturer's instructions, including the dosage recommended by the manufacturer. The package insert of the drugs used (anticion and inibidex) indicated that the dose should be 50 mg/cat, regardless of weight. Therefore, the drugs were administered at this dosage to all the queens in the experimental group.

In the control group (CG), saline solution was administered in the same volume (1 mL) as the contraceptive administered to AG cats subcutaneously in the right lateral abdominal region.

Thirty days after the administration of contraceptives, all cats were examined, and examinations performed during the initial consultation were repeated. Ninety days after contraceptive administration, all cats underwent ovariohysterectomy.

The data were analyzed by determining the absolute (n) and relative (%) frequencies.

Results and Discussion

In a previous case report, we found that a single application of medroxyprogesterone was sufficient to cause MH in a female cat (Oliveira et al., 2014). However, most articles published in the literature are case reports. Unfortunately, only few studies have assessed the use of these medications, especially in feline species. Therefore, the present study was designed to observe the effects of controlled experimental administration of contraceptives, including a control group.

The use of contraceptive medication, even once, increases the risk of developing diseases associated with this type of medication and should be discouraged by veterinarians and replaced whenever possible by castration surgery (D. C. B. C. Silva, 2020). Thus, the present study was conducted with the objective of providing information about the administration of contraceptives in cats under the same conditions practiced by the owners.

All queens were of a mixed breed. Most of the female cats included in the study were up to three years old and were considered young adults.

When the queens were examined at 30 days, no changes were observed in blood counts or ultrasound examinations. However, on physical examination, all cats in the contraceptive group (100%) showed volume enlargement of the mammary glands (Figure 1). The increase in volume was verified by visual inspection and careful palpation of the mammary glands. The cats in the control group showed no detectable macroscopic changes in the mammary glands or any other organ systems.

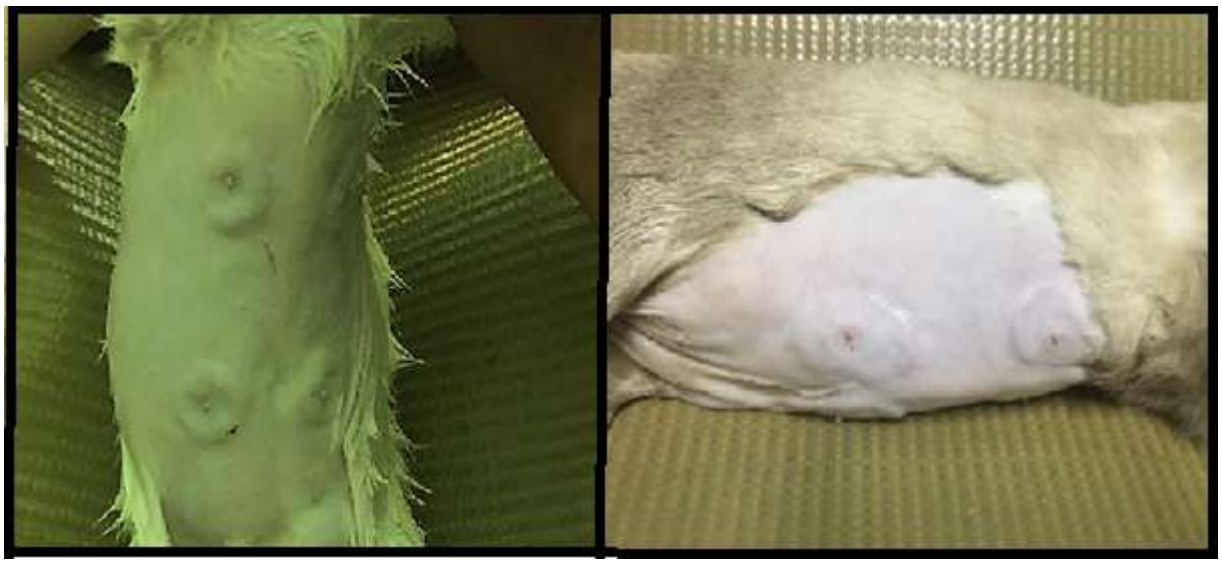

Figure 1. Increase in mammary glands volume after 30 days of progestin administration in healthy cats.

In the clinical evaluation performed on all cats 90 days after contraceptive administration, no female cats showed detectable clinical changes in any examinations (clinical examination, blood count, and ultrasonography). In cats that presented with volume enlargement of the mammary glands (100% of the cats in the AG), the pathological alteration showed regression, and these females were clinically normal. Regression was verified by visual inspection and careful palpation of the mammary glands. Microscopic examinations were not performed because of the refusal of owners to undergo a biopsy. It is important to note that cytological and histopathological examinations were not offered at the service where the experiment was conducted. Therefore, owners were required to pay for examinations that would be outsourced. Unfortunately, the owners refused to pay for the scans due to financial concerns. In addition, some owners claimed that the examinations could cause pain and did not authorize them.

Literature suggests that some conditions presented by cats can be aggravated by the administration of contraceptives. These conditions include diabetes, mammary gland lesions or tumors, and cystic endometrial hyperplasia (Romagnoli, 2002). Given this information, it was important to conduct tests that ruled out these conditions in the queens in this study. To exclude such conditions, an anamnesis, physical examination, blood count, biochemical tests (urea, creatinine, and alanine aminotransferase), and abdominal ultrasonography were performed on all cats. Only cats that did not show detectable changes on these examinations were selected to avoid bias that could have altered the results of the study.

It is possible that the increase in the volume of the mammary glands in cats was hyperplasia. However, confirmation of such an alteration was not possible because tests that could confirm the disease were not performed, such as the cytology and histopathology tests recommended in the definitive diagnosis of hyperplasia (Dyulger et al., 2020). However, this condition can be suspected because some authors believe that the disease can be diagnosed clinically (F. B. Silva et al., 2012). Such examinations were not performed on the female cats in this study because of the financial limitations of the owners and the welfare of the females.

Mammary enlargement observed in all cats in the AG group was due to the action of the progestogen on the mammary gland. According to Kennedy (2018), one of the functions of progesterone is to promote the development of the alveolar tissue of the mammary glands.

Although the enlargement of the mammary glands presented by the cats that received contraceptives regressed, it cannot be said that the mammary tissue had not suffered any pathological changes since microscopic examinations (cytology or histopathology) and immunohistochemistry were not performed.

As observed in the present study, in which the owners did not consult veterinarians regarding the decision to buy contraceptives for the reproductive control of their queens, several authors commented that the majority of owners in Brazil administer these medications at home (Melo et al., 2021; D. C. B. C. Silva, 2020) and

without the indication of a veterinarian (D. C. B. C. Silva, 2020). Some authors claim that the wide use of contraceptive medications in animals can be justified by the lack of need for a prescription because they are easily found in veterinary pharmacies owing to their low cost and ease of administration, even in injectable forms (Melo et al., 2021; D. C. B. C. Silva, 2020)

The strongest suspicion related to the mammary changes observed in cats in this study was the occurrence of MH. This suspicion is based on the fact that MH is the most common disease that can result from contraceptive administration in cats. Several authors have reported the occurrence of MH after the administration of contraceptives in female cats (Araújo et al., 2014; Loretti et al., 2005; Melo et al., 2021; Oliveira et al., 2014), strengthening the suspicion that the female cats in the study showed such alterations.

Although cats subjected to a single administration of synthetic progestogen may present with MH (Loretti et al., 2005), it was not possible to affirm that the cats in the present study presented such alterations. An increase in the volume of the mammary glands was observed after contraceptive administration, with regression of the condition after 90 days. It is likely that feline MH occurs more commonly after prolonged use of progestogens because the accumulation of exogenous hormones, which can remain stored for months in the animal's body, leads to late mammary changes (Robinson & Noakes, 2018). The cats included in this study had not previously received any contraceptives.

One factor that must be considered to ensure the safety of contraceptive administration is the dose used in animals. The literature demonstrates that calculating the dose considering the weight of the animal leads to a lower risk of adverse effects (Romagnoli, 2002). However, some Brazilian veterinary progestogen package inserts have a single indication of a dose of 50 mg/cat per application (Anticion, 2021; Inibidex, 2023). Thus, adverse side effects can be maximized at higher doses. In this study, the drugs were administered to the cats as per the dose prescribed in the package leaflet, since the study methodology predicted that contraceptives should be administered as it is used in practice. Thus, the administration of contraceptives as carried out by owners and clerks characterizes medication without medical-veterinary guidance, a conduct that is common in Brazil (Zielke et al., 2018; Amorim et al., 2020). Consequently, there are important causes of drug intoxication in veterinary services in Brazil, including in felines (Amorim et al., 2020).

For the safe use of contraceptives in cats, it is important that the drug be administered when the animal is in anestrus (Romagnoli, 2015). However, the estrous cycle phase of bitches and cats can only be assessed using vaginal cytology (L. D. M. Silva, 2016), which is restricted to veterinarians. Therefore, contraception is often used during other periods of the estrous cycle. Their indiscriminate administration, in addition to not promoting the desired protection, greatly increases the risk of developing diseases related to these hormones, and methods to control the sale and application of these drugs must be developed (D. C. B. C. Silva, 2020). It is important to emphasize that contraceptives are included among the drugs used without veterinary medical guidance (Zielke et al., 2018).

The frequency of contraceptive administration is another point that must be analyzed. In a study conducted in the metropolitan region of João Pessoa (PB), most owners were unable to inform how often they administered the medications, and only 25% did every four months, which is the recommendation of the package insert of these medications for constant estrus inhibition in felines. These data show how the use of contraceptives in cats is indiscriminate and random and justify the frequency with which they are affected by the side effects of these drugs (D. C. B. C. Silva, 2020).

MH in cats is treated through ovariohysterectomy (Loretti et al., 2005; Melo et al., 2021), which was performed in the queens 90 days after drug administration. However, mammary enlargement had already shown regression.

Conclusion

A single application of an injectable contraceptive (label dose) in female cats caused macroscopic mammary changes suggestive of MH. It is suggested that such medications should be prescribed exclusively by veterinarians.

Acknowledgments

The authors thank the Universidade Paranaense (UNIPAR) for financial support in conducting this study.

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