Cabergoline versus Bromocriptine for oestrus induction in female dogs

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Abstract

This study aimed to evaluate two protocols of oestrus induction, using different anti-prolactin dopamine agonists (cabergoline, bromocriptine) in domestic bitches. For this purpose, 16 females previously followed were divided into two experimental groups: Group A, bromocriptine induction group (n=8; 0.05 mg/kg/day/orally) and group B, cabergoline treatment group (n=8; 0.005 mg/kg/day/orally). Comparison of the effects of the two substances included several parameters (oestrus induction, pregnancy, and whelping rates, litter size, treatment duration, shortening of inter-oestrus interval, and effect on duration of the inter-oestrus interval following the induced cycle). Cabergoline was more efficient than bromocriptine with induction, pregnancy and whelping rates of 87.5% versus 25%, respectively (P<0.05). The mean duration of cabergoline treatment was 24.43 ± 7.77 days with a range from 16.66 to 32.20 days, as opposed to a duration of 34.50 ± 6.86 days and range from 27.64 to 41.36 days for bromocriptine. Moreover, cabergoline reduced the inter-oestrus interval in normal cycled bitches by a mean duration of 43.40 ± 14.30 days and a range from 29.10 to 57.70 days, while no significant shortening of this interval was observed with bromocriptine. For litter size, no significant difference was observed between values before and after induction treatments. Neither drug significantly affected the inter-oestrus interval after the induced cycle. Cabergoline treatment was therefore more effective and safer than bromocriptine for inducing fertile oestrus in domestic bitches followed by normal pregnancy, whelping and litter size and also a normal post induction inter-oestrus interval. It also has an easier administration protocol and fewer side effects. In addition, cabergoline was more efficient in inducing oestrus in females with a long inter-oestrus and in those presenting primary and secondary anoestrus with no extra gonadal causes.

Key words: *bitch; treatment; cabergoline; bromocriptine; oestrus cycle*

Introduction

Oestrus induction in bitches offers several advantages such as controlling the timing of pregnancy, treating prolonged infertility or anoestrus, failure of conception or losing of breeding, and synchronising ovulation for artificial insemination

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and embryo transfer programmes (Jaafar and Al-Mutar, 2024). Given its importance in female dogs, many studies have been conducted in order to develop induction protocols using different substances and combinations: oestrogens, pituitary gonadotropic hormones (FSH, LH), exogenous gonadotropins (equine Chorionic Gonadotropin [eCG], Human Chorionic Gonadotropin [HCG]), dopamine agonists, and GnRH agonists (Nagashima et al., 2021). They have all presented some limits related to the wide variation and the conflictual results regarding the success rates obtained. Approaches using eCG and hCG rarely exceeded 50% fertility rates and 20–30% pregnancy rates (Kutzler, 2005). FSH alone gave less satisfactory results, its association with a synthetic oestrogen (diethylstilbestrol) relatively improved the results with 70% induction rate and 46% ovulation, but only 20% gestation (Buff, 2001). The administration of GnRH and its analogues can only be used if the functioning of the pituitary-ovarian axis is preserved (Kutzler, 2005). It should also be revealed that some protocols are unsuitable for the clinical veterinary field due to their cost or labour intensity (Bolghanabadi et al., 2023).

The administration of anti-prolactin substances ("dopamine agonists" such as cabergoline or bromocriptine) was associated with an increase in basal plasma FSH concentration, resulting in the shortening of the inter-oestrus interval or inducing oestrus in case of prolonged anoestrus (Okkens et al., 1997; Ohtaki et al., 2020). Therefore, their use has opened a new possibility for oestrus induction in the bitch. They currently represent the best tool for establishing an oestrus induction protocol in terms of efficacy, safety, simplicity, and cost (Gobello et al., 2001). Many comparative studies have evaluated the efficacy of different induction protocols in the bitch using anti-prolactin molecules. Cabergoline has been evaluated compared to Busereline (GnRH agonist) in clinical trials and has proven to be practically more effective (Rota et al., 2003). Another study on oestrus induction using anti-prolactin drugs and levothyroxine was performed by Ajitkumar et al. (2010). More recently, another protocol combining cabergoline and eCG was designed. With this association, follicle growth showed good results but the pregnancy rate was low (Bolghanabadi et al., 2023). In Iraq, Abdal-Hadi Nawaf and Ibrahim, (2019) while experimenting with bromocriptine and cabergoline in old dogs, found significant differences in time to oestrus and conception rates between treatments.

In the current study, the objective was to comparatively evaluate the clinical efficacy of two treatment protocols based on these two molecules in oestrus induction in domestic dogs (*Canis familiaris*) in Algeria. The comparison was made in view of several criteria, namely induction rate, pregnancy rate, birth rate, litter size (prolificacy), duration of treatment, shortening of the inter-oestrus interval (shortening of anoestrus), and the effect on the duration of inter-oestrus following the induced cycle (return to heat after the induced cycle).

Materials and Methods

Animal management & study area

The animals included in the study consisted of 16 female dogs of various breeds (10 German Shepherds, 2 Belgian Malinois, 1 Doberman, 1 Atlas Shepherd, and 1 Sloughi), aged 4.63 ± 0.53 years and weighing 25.81 ± 1.53 kg (Mean ± SE). They were housed in individual kennels at the Canine Training and Breeding Centre of Baïnem (Algiers, Algeria), in a system designed to fully comply with sanitary conditions and psychological comfort. They were fed a single daily ration of super-premium quality,

industrial dry food and had access to water *ad libitum*. For each female, a complete medical and administrative file was available. The medical follow-up since the arrival of each dog at the centre was included in each individual file. It contained the monthly weighing, vaccination dates, pathological history accompanied by treatments, and breeding career (dates of heat and mating, male(s) used for mating, dates of whelping, and litter sizes).

Outside the framework of this experiment, the animals were subject to periodic health monitoring and continuous medical checks provided by the Veterinary Service.

Exclusion criteria for this study: young females that have not yet shown signs of oestrus, bitches over seven years old, bitches presenting any pathology of a general nature or affecting the reproductive system. We excepted cases of primary and secondary anoestrus without extra-gonadal causes, which were kept in the experiment for study purposes.

Experimental design

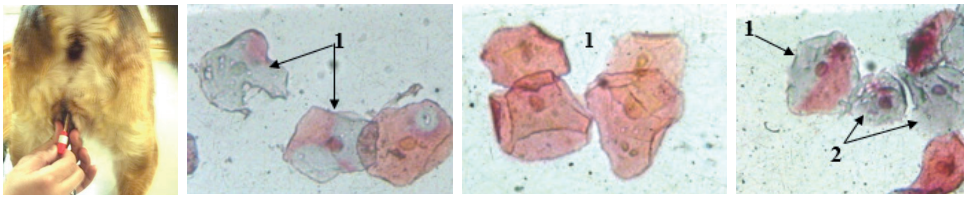
The experiment was divided into two phases: preliminary monitoring period (4.5 months) and an induction period (6 months).

Preliminary monitoring

Preliminary monitoring of 16 females was conducted through bi-weekly visits, which included clinical examination, vaginal cytology, and blood sampling for subsequent progesterone (P4) determination. Dogs were individually subjected to a general clinical examination and then a special examination of the genital tract to look for clinical and behavioural signs of heat.

At each visit, all animals systematically underwent a vaginal smear (Figure 1). Once the vaginal cells were collected, the cotton swab was immediately rolled on the end of a microscope slide which was immersed for five minutes in an alcohol-ether mixture for fixation. The slide was stained according to the Harris-Schorr trichrome method (Schutte, 1967; Corvelyn et al., 2022) using the kit Accustain® Harris Hematoxylin Solution (Sigma-Aldrich, United Kingdom). Cell counting was performed based on a minimum of 30 epithelial cells. For this, the slides were viewed at a higher magnification (x100 and/or x400). Microphotographs of these slides were captured using a Moticam 350 microscope camera and professional Motic Images Plus software (Version 2.0, ML Motic China Group Co., Ltd.).

For P4 analysis, blood samples were collected from the radial vein using a vacutainer device on a pre-identified heparinised vacuum tube, centrifuged and stored at -20°C until analysis. Plasma samples were analysed at the Zootechnics Laboratory of the Draria Nuclear Research Centre (Algiers, Algeria) using a radioimmunoassay



Vaginal smear

Proestrus
(1: Large intermediate polychromatophilic vaginal cells (x400)

Oestrus
(1: Keratinised superficial cells (eosinophils) (x400)

Metoestrus
(1: Reappearance of large polychromatophilic intermediates; 2: Reappearance of basophilic intermediates) (x400)

Figure 1. Vaginal cytology for cycle staging and evaluation

method (Kit Immunotech, Beckman Coulter Company, France)

The aim of the preliminary study was to evaluate the cyclicity of the animals and to better understand their vaginal cytology and progesterone profiles before starting the experiment (oestrus induction). In addition, it allowed for a relatively reliable calculation of their previous inter-oestrus intervals based on the data collected in their files and from this preliminary follow-up, and to choose the right time to introduce the two induction treatments simultaneously to both groups A and B.

Induction period

Prior to the oestrus induction treatments, the 16 animals were divided into two experimental groups of eight females each (Table 1). Group A received bromocriptine, while Group B was treated with cabergoline. The constitution of the groups was carried out according to the following study criteria: females known for having prolonged inter-oestrus intervals (without pathological condition) showing hypo-prolificacy, as well as animals presenting a problem of primary or secondary anoestrus were selected and distributed equally into the two groups for the induction trials. The purpose was to evaluate the efficacy of the induction treatment in case of an abnormally prolonged inter-oestrus interval and in the case of primary and secondary anoestrus. The groups were constituted in such a way as to encompass all three stages of anoestrus (beginning, middle and end of anoestrus) during the induction treatment protocols.

The reproductive history and preliminary monitoring data allowed us to select eight dogs presenting cyclicity abnormalities which included: four females presenting a very long inter-oestrus interval al-

Table 1. Constitution of treatment groups according to reproductive state

Group	Code	Stage of cycle at the beginning of treatment
A	2	Metestrus
	3	Beginning of anoestrus
	6	Mi-anoestrus
	7	End of anoestrus
	13	Anoestrus (long inter-oestrus)
	14	Anoestrus (long inter-oestrus)
	1	Primary anoestrus
	8	Secondary anoestrus
B	12	Metestrus
	4	Beginning of anoestrus
	11	Mi-anoestrus
	10	End of anoestrus
	15	Anoestrus (long inter-oestrus)
	16	Anoestrus (long inter-oestrus)
	5	Primary anoestrus
	9	Secondary anoestrus

though still within the physiological limits reported in the literature; two in primary anoestrus, and two in secondary anoestrus.

Induction treatment began simultaneously on the same day for both groups. Group A received bromocriptine (Parlodel® 2.5 mg tablets, Novartis) progressively at a dose of 0.05 mg/kg live weight per day orally, while group B received cabergoline orally at a dose of 0.005 mg/kg, equivalent to 0.1 ml per kg live weight of a 15 mL Galastop® product (Galastop® oral solution 15 mL, CEVA Santé Animale; Manufacturer: VETEM Sp.A., Italy). The therapeutic approach continued until signs of proestrus appeared or for a maximum of 40 days (Concannon, 1993). Specifically, for bromocriptine, this molecule was introduced gradually, starting with a low dose of 0.6 mg/female for three days and then progressively increased until reaching the full dose (0.05 mg/kg) in order to avoid the emetogenic effect of bromocriptine, as previously indicated in the literature (Verstegen et al., 1999).

Clinical, cytological, and hormonal monitoring was performed on all experimental females throughout the study. During the treatment period, these two groups were housed and monitored separately to avoid any sensory cross-influence that could compromise the induction results.

Treatment positivity evaluation

For the bromocriptine induction protocol, the female was considered to have responded to the induction treatment if it showed clinical, cytological and hormonal signs (assessed *a posteriori*) of proestrus in the period extending from the first day of treatment until 15 days after the end of treatment, i.e., 55 days from the start of treatment. For the cabergoline induction protocol, the dog was considered to have positive response to treatment if it showed clinical, cytological and hormonal signs (assessed *a posteriori*) of proestrus in the period extending from the first day of treatment until 40 days (Concannon, 1993).

Cycle monitoring during and after induction treatment

Oestrous cycle monitoring during and after induction treatment allowed us to assess the effectiveness of this treatment by triggering oestrus with ovulation, followed by conception and gestation that resulted in the birth of healthy puppies.

Clinical, cytological and hormonal monitoring was performed for all females in the experiment throughout the study period, however cytology and blood sampling for P4 evaluation were stopped once gestation was confirmed. Gestation was clinically monitored until parturition to collect data related to pregnancy and birth rates, as well as litter size. The date of appearance of the female's next proestrus was noted to assess the return to heat after the induced cycle (assessing the duration of the inter-oestrus interval of the cycle following the induced one).

Ethical Statement

All animal studies were conducted with the utmost regard for animal welfare, and all animal rights issues were appropriately observed. No animal suffered during the course of this study. All experiments were carried out according to the guidelines of the Institutional Animal Care Committee of the Algerian Higher Education and Scientific Research (Agreement Number 45/DGLPAG/DVA.SDA. 14).

Statistical Analysis

Statistical analysis of the data was carried out using STATISTICA software (Version 10, Stat Soft France, 2003). After a descriptive analysis and in order to compare the results of the two induction treatments according to all the parameters mentioned above, Fisher's exact test was

Table 2. Comparison results of the two induction treatments in 16 dogs

	Group A (*Bromocriptine*)		Group B (*Cabergoline*)	
Result	***n***	**%**	***n***	**%**
Success	2	25.00	7	87.50
Failure	6	75.00	1	12.50
Total	8	100	8	100

***P* value (Fisher's test):** 0.02097902 ($P<0.05$)

applied. Data were presented as mean ± SE, and the significance level was set at 5%.

Results and Discussion

Comparison of oestrus induction, pregnancy and birth rates

The comparison of the two induction treatments (bromocriptine versus cabergoline) in the 16 female dogs are presented in Table 2. The induction, pregnancy and birth rates gave the same values for both treatment groups (A and B). These values were identical for these three variables because all females that responded to the induction treatment ovulated normally, were fertilised, maintained their pregnancies under normal conditions, and gave birth to puppies. Therefore, the induction rate in this study can also be considered as the ovulation rate.

For the comparison between the groups, our results showed that the success rate with cabergoline (B) (87.50%; 7/8) was higher than that obtained with bromocriptine (A) (25%; 2/8) ($P<0.05$).

Our data for induction, gestation and birth rates with cabergoline treatment are similar to those reported in Belgium (Jeukenne and Verstegen, 1997). They found an induction rate of 80% with gestation and birth rates of 60%. The discrepancy between the induction and gestation rates suggested the presence of an anovulatory oestrus in animals, which was not observed in this study. In the same study, a 100% cabergoline induction rate was achieved for two additional groups (n=5), with a pregnancy rate of 80% and an overall induction and pregnancy rate of 100%. The small sample size could have contributed to the amplification of induction results in that experiment. Moreover, our data are consistent with those reported by Rota et al. (2003) in Italy. These authors conducted a comparative study of two induction protocols (cabergoline versus buserelin) and revealed an induction, gestation, and birth rate of 83% for 12 females in the cabergoline group. Similarly, our results aligned with those reported by Zöldág et al. (2001) in Hungary, who reported an induction, gestation, and birth rate of 84.6%. However, the dose of cabergoline used in their study was much higher (6 mg/kg/day for 14 days), as the work aimed to evaluate the effect of dose on treatment duration. In Türkiye, Cırıt et al. (2007) achieved an induction rate of 80% and a pregnancy rate of 60% in a sample of 10 females subjected to a cabergoline induction protocol identical to our work.

For bromocriptine induction treatment, our results are different to those reported in the literature: a gestation rate of 62% after four months of treatment (40 µg/kg/d) was reported by van Haaften et al. (1989). Concannon (1993) reported a bromocriptine induction rate of 80%, but the gestation rate was not determined. In other studies, induction rates obtained were associated

with fairly long treatment periods, ranging from 92±11 to 136±16 days (Tainturier et al., 1994; England and Hewitt, 1999). This revealed a real problem due to the particularly emetogenic side effects of this molecule (Bolghanabadi et al., 2023).

In the same context, comparing both treatments (with different doses to those used in our trials) in a study in India, Bisen et al. (2021) reported an oestrus induction rate of 85.70% vs 71.48%, a conception rate of 100% vs 75%, with a whelping rate of 100% in bitches receiving up to 20 days cabergoline and bromocriptine. In addition to these dopamine agonists, those authors experimented with additional molecules. In old dogs, Abdal-Hadi Nawaf and Ibrahim (2019) found significant differences in conception rates between the two treatments.

Comparison of other reproductive parameters

Aside from the three success percentages analysed above, the other variables in Table 3 and 4 are quantitative, with numerical values expressed in terms of the number of days and the number of puppies.

For the "litter size" variable, comparing the data obtained for each treatment group with the pre-induction, no significant dif-

Table 3. Pre-treatment reproduction data for the two induction groups (Mean ± SE)

Group	Average age (years)	Average weight (kg)	Previous litter size (number of puppies)	Previous inter-oestrus duration (number of days)	
Group A (*n*=8)	4.50 ± 0.74 [3.67 – 5.24]	26.38 ± 2.09 [24.28 – 28.47]	5.00 ± 0.51 [4.49 – 5.51]	215.33 ± 56.14* [159.19 – 271.48]	170.50 ± 11.66** [158.84–182.16]
Group B (*n*=8)	4.75 ± 0.81 [3.94 – 5.56]	26.00 ± 2.54 [23.46 – 28.54]	5.83 ± 0.60 [5.23 – 6.44]	204.17 ± 33.02* [171.15–237.18]	178 ± 12.30** [166.45 – 191.05]

(*): These values for the inter-oestrus duration variable were calculated based on all females, including those with prolonged inter-oestrus, specifically females (13) and (15) in Group A and females (15) and (16) in Group B. Consequently, these values were abnormally high. (**): These values for the inter-oestrus duration variable were calculated excluding females with prolonged inter-oestrus. Thus, these data reflected the normal cyclicity of the females.

Table 4. Induction results for the two groups: Group A, bromocriptine (50 µg/kg) and Group B, Cabergoline (5 µg/kg)

Group	No. responses + / Induction rate	No. responses +/ Gestation rate	No. responses +/ Birth rate	Treatment duration (No. days)	Shortening of inter-oestrus interval (No. days)	Litter size (No. puppies)	Post induction inter-oestrus (No. days)
Group A	2/8 --- 25%	2/8 --- 25%	2/8 --- 25%	34.50 ± 6.86 [27.64 – 41.36]	6.75 ± 9.31 **NS*** [(-2.56) – 16.06]	5.50 ± 0.98 [4.52 – 6.48]	200.00 ± 34.24 [165.76 – 234.24]
Group B	7/8 --- 87.50	7/8 --- 87.50	7/8 --- 87.50	24.43 ± 7.77 [16.66 – 32.20]	43.40 ± 14.30 [29.10 – 57.70]	5.86 ± 0.79 [5.07 – 6.65]	186.29 ± 8.87 [177.42 – 195.15]

(*): NS: Not significant because the confidence interval included 0 [(-2.56) – (16.06)]. This indicates that the average was based on only two values, which were too dispersed. Therefore, it will not be considered.

ference was found, although the result was less representative for the bromocriptine group due to the low number of induced females. Therefore, it is unnecessary to compare these results between the two treatment groups. Contrary to literature reports (Verstegen et al., 1999), the two anti-prolactin induction treatments (bromocriptine and cabergoline) had no influence on litter size in the present study, which concurs with another recent experiment (Bisen et al., 2021). The latter mentioned similar numbers after oestrus induction for both groups. Similarly, no difference in number of puppies born was obtained by Abdal-Hadi Nawaf and Ibrahim (2019).

In the bromocriptine induction group, the two induced females experienced a shortening of the inter-oestrus interval by 11.5 days and 2 days, respectively, with a mean of 6.75 ± 9.31 days [NS] and a confidence interval of [(-2.56) - 16.06]. This result is not significant because the confidence interval included zero. Therefore, this treatment did not record a significant shortening of the inter-oestrus interval. In contrast, the cabergoline induction group experienced a mean shortening of the inter-oestrus interval of 43.40 ± 14.30 days, with a confidence interval of [29.10 - 57.70]. For this average, the two anoestrus females were excluded. In the literature, much greater reductions in the inter-oestrus interval have been reported (Gobello et al., 2001).

With the exception of Concannon (1993) and van Haaften et al. (1989), who reported a treatment duration of 17–28 days, and of 47 ± 2 days, respectively, previous data mentioned long treatment periods ranging from 92 ± 11 to 136 ± 16 days (Tainturier et al., 1994; England and Hewitt, 1999). In our case, the two females induced with bromocriptine responded after 38 and 34 days of treatment, respectively, with an average of 34.50 ± 6.86 days and a range of [27.64 - 41.36]. This result, which deviated from the findings of most studies, was not very representative of the study group (two induced females out of eight treated). From a practical perspective, and based on our observations during this clinical trial, we believe that prolonged treatment with bromocriptine is prevented by the predominantly emetic side effects of this molecule at the study dose, despite any attempt of gradual introduction.

As for the duration of induction treatment with cabergoline, our mean of 24.43 ± 7.77 days, with a confidence range of [16.66-32.20], is close to the values reported in the literature for the same treatment protocol in terms of dosage used. Specifically, periods of 23.5 ± 3.2 days and 23.5 ± 5 days of treatment have been reported previously (Arbeiter and Barsch, 1988; Rota et al., 2003, respectively). Much shorter treatment durations have been reported; Gobello et al. (2001) in Argentina, reported a treatment duration of 16.2 ± 2.7 days, while Zöldág et al. (2001) mentioned values ranging from 6 to 14 days. These low values can be explained by the dose of cabergoline used which was much higher than that administrated in our experiment (6 mg/kg/day).

In the present study, we identified another factor influencing treatment duration: the stage of anoestrus at the start of induction treatment. Specifically, in the cabergoline induction group, the treatment durations for females starting cabergoline at the beginning, middle, and end of anoestrus were 32, 20, and 12 days, respectively. These results align with those obtained by Verstegen et al. (1999), who reported treatment durations of 20 ± 3 days, 14 ± 3 days, and 6 ± 1 days for females treated at the beginning, the middle, and the end of anoestrus. Finally, in our study, this comparative evaluation criterion of the two induction treatments is in favour of the cabergoline protocol and disadvantages the bromocriptine treatment.

Our results showed that the induction treatment with either bromocriptine or cabergoline did not significantly affect inter-oestrus following the induced cycle in treated females. Therefore, they would return to heat within the usual timeframe. In the bromocriptine induction group, the two induced dogs had an inter-oestrus interval following the induced cycle of 184 and 170 days, respectively, compared with 177.5 and 170 days, with a difference of 6.5 and 11 days, respectively. These two females returned to heat within a timeframe similar to that of their previous cycles. In the cabergoline induction group, with the exception of the two animals with primary and secondary anoestrus, the five dogs had inter-oestrus intervals following the induced cycle of 170, 185, 189, 191, and 177 days, compared with 163.5, 181, 182, 230.5, and 287 days, respectively, with a difference of 6.5, 4, 7, -39.5, and -110 days, respectively. Among these five females, three were regular-cycled; the inter-oestrus intervals following the induced cycle were unchanged from the previous intervals recorded in the reproduction information of the females. On the other hand, the other two dogs experienced a shortening of their prolonged inter-oestrus intervals, as they were irregular-cycled with the issue of a long but physiologically normal inter-oestrus (<12 months). This finding suggested that induction treatment in a regular-cycled female did not alter the inter-oestrus following the induced cycle. In the long inter-oestrus dog, induction treatment considerably reduced this interval. According to this result, the comparative evaluation of the two induction treatments in our study and their effect on the inter-oestrus interval following the induced cycle revealed no significant difference between the two molecules.

In group B, two of the induced females had a long inter-oestrus interval of 270 days and 221 days, respectively, and both responded to treatment after 18 and 16 days of cabergoline administration. On the other hand, in the group A, the two animals with long inter-oestrus intervals of 229 days and 297 days, respectively, failed to respond to induction treatment. Our data showed that cabergoline was more effective than bromocriptine in inducing oestrus in females with long inter-oestrus intervals, provided that the condition did not involve secondary anoestrus, i.e., without exceeding 12 months of anoestrus.

It is well known in dogs that anoestrus can be either primary (bitches that never had an ovarian cycle) or secondary (bitches that had one or more ovarian cycle but subsequently failed to cycle). The latter could occur after the onset of endocrine and non-endocrine disorders (Bisen et al., 2021). In group A (bromocriptine treatment), no response to induction was recorded in two females (one each with primary or secondary anoestrus) that had not shown heat for 478 days, approximately 16 months of anoestrus. In group B, both the female with primary and secondary anoestrus, each in anoestrus for 536 days, approximately 18 months, responded to the induction by cabergoline after 40 days and 33 days of treatment, respectively. Our results indicate that this drug was more effective than bromocriptine in inducing oestrus in females with primary or secondary anoestrus. However, it was essential that these females underwent a thorough investigation of their anoestrus before any induction treatment to rule out any specific underlying causes that might require specialised therapeutic measures. In our study, females with primary and secondary anoestrus were extensively investigated clinically and biologically prior to experimentation as part of their medical management. Induction was considered a last resort after ruling out any extra-gonadal causes of

anoestrus. They were equally distributed between the two induction groups in our study, with the aim of attempting to induce oestrus and restore reproductive function. In addition to these evaluation criteria used to comparatively study the two induction protocols, we also considered the factors of treatment side effects, as well as the ease of preparation, measurement, and administration of the daily dose.

Side effects of each treatment

From the outset of treatment, bromocriptine exhibited a strong emetic effect on nearly all females treated. To avoid potential competitive antagonism, no anti-emetics were used in our experiment, as specific anti-emetics act through the same dopamine D2 receptors channel (Okkens et al., 1997). The emetic side effects observed in our study are consistent with those reported in the literature (Gobello et al., 2001). Despite the progression observed in the application of the treatment protocol, the emetic effect did not completely subside.

In group B, no such effects were recorded, and the daily dose was very well tolerated by females. Cabergoline seemed to be better tolerated at the dose used (0.005 mg/kg/d) compared to bromocriptine (0.05 mg/kg/d). This finding is in accordance with previous reports, which highlighted cabergoline's selective action with fewer effects on the central nervous system compared to those caused by bromocriptine. More particularly, it presents a high rate of specificity for D2 receptors and a long-lasting effect on pituitary lactotropic cells (Wildemberg et al., 2021; Bolghanabadi et al., 2023).

It is clear that our result is in favour of cabergoline for oestrus induction protocols. Bromocriptine is disadvantaged due to its side effects, particularly its emetogenic effect, which can make its use problematic. This issue is exacerbated by the long treatment durations required and the inability to use specific antiemetics due to their competitive antagonism with dopamine D2 receptors.

Under the conditions of this experimental study, it can be concluded that cabergoline treatment is clinically more effective than bromocriptine in inducing fertile oestrus followed by pregnancy and parturition. Additionally, it shortened the inter-oestrus interval in females with normal cyclicity. In contrast, no shortening of this interval was observed with bromocriptine in the two induced females. For average prolificacy or average litter size, no significant difference was recorded between the previous farrowing and the farrowing of the induced cycle.

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Kabergolin u usporedbi s bromokriptinom za induciranje estrusa u kuja

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Cilj je ove studije bio procijeniti dva protokola induciranja estrusa, uporabom različitih anti-prolaktinskih agonista dopamina (kabergolina i bromokriptina) u kuja. U tu svrhu korišteno je 16 prethodno praćenih ženki koje su dodijeljene u dvije eksperimentalne skupine: skupinu A, skupinu s indukcijom pomoću bromokriptina (n=8; s 0,05 mg/kg/dan/oralno) i skupinu B, skupinu tretiranu kabergolinom (n=8; s 0,005 mg/kg/dan/oralno). Statistički komparativna procjena između dvije molekule uključivala je nekoliko parametara (induciranje estrusa, trudnoća i stope porođaja, veličina okota, trajanje tretmana, skraćivanje intervala između estrusa i učinak na trajanje intervala između estrusa nakon induciranog ciklusa). Podatci su pokazali da je kabergolin bio učinkovitiji od bromokriptina s induciranjem, trudnoćom i stopom porođaja od 87,5 % u usporedbi s 25 % (P<0,05). Srednje trajanje tretmana kabergolinom bilo je 24,43±7,77 dana s rasponom od 16,66 do 32,20 dana u usporedbi s trajanjem od 34,50±6,86 dana i rasponom od 27,64 do 41,36 dana za bromokriptin. Nadalje, kabergolin je skratio interval između estrusa u kuja s normalnim ciklusom za srednje trajanje od 43,40±14,30 dana i rasponom od 29,10 do 57,70 dana dok s bromokriptinom nije zamijećeno značajno skraćivanje tog intervala. Za veličinu okota nije zamijećena značajna razlika između vrijednosti prije i nakon tretmana za induciranje. Niti jedan lijek nije značajno utjecao na interval između estrusa nakon induciranog ciklusa. Zaključno, u uvjetima ove studije, tretman kabergolinom bio je učinkovitiji i sigurniji od bromokriptina za induciranje plodnog estrusa u kuja nakon kojeg je uslijedila normalna gravidnost, porođaj i veličina okota, kao i normalni interval između estrusa nakon induciranja. Kabergolin je osigurao i daleko lakšu primjenu protokola i manje nuspojava. Uz to, bio je i učinkovitiji u induciranju estrusa u kuja s dugim razdobljem između estrusa i onih koje su pokazivale primarni i sekundarni anestrus bez dodatnih uzroka od strane jajnika.

Ključne riječi: *kuja, tretman, kabergolin, bromokriptin, ciklus estrusa*