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RESEARCH ARTICLE

Induction of estrus in bitches with the dopamine agonist bromocriptine

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Abstract

The number of described reliable and practicable methods for the control of the estrous cycle of the dog are limited.

The aim of this study was to test for estrus induction in bitches using bromocriptine. 23 bitches in anestrus stage were treated with 0.025 mg/kg/d bromocriptine (Bromocriptine®, Sopharma, Bulgaria) orally for three days, followed by 0.05 mg/kg/d for three days and then 0.1 mg/kg/d until day 5 after onset of proestrus. To avoid side effects, like vomiting, the daily dose was divided into two and given in the morning and in the evening. Estrus induction was successful in 22 (95.65%) bitches with a variation of 4 to 49 days until first signs of proestrus occured (vulvar bleeding) (mean 22.86±12.34 days); no estrus signs were observed in one bitch (4.35%) until day 56. Mating of the 22 bitches twice in their fertile periods determined using vaginal cytology and serum progesterone levels resulted in intact pregnancies in 19 animals (86.35%). The number of puppies ranged between 2 and 11, with an average litter size of 5.00±2.36.

Our results confirm previous observations that bromocriptine offers a suitable option for induction of fertile estrus.

INTRODUCTION

There are many indications for estrus induction in the bitch, mainly including treatment of prolonged anestrus or infertility, missed breeding opportunities or conception failure, planning a particular mating at the time around the availability of the stud dog, synchronization of ovulation for embryo transfer programs and to control the timing of pregnancy and whelping under research laboratory conditions (Kutzler, 2007).

Methods for canine estrus induction described in literature include the use of synthetic estrogens (diethylstilbestrol), GnRH agonists (lutrelin, buserelin, fertirelin, deslorelin and leuprolide), exogenous gonadotropins (LH, FSH, hCG, PMSG and human menopausal gonadotropin) and dopamine agonists (bromocriptine and cabergoline) (Kutzler, 2005); however, with cabergoline and deslorelin being those ingredients most widely used in clinical practice in various countries.

The interestrus interval in the bitches of different breeds varies between 16 and 56 weeks (average 31 weeks) (Christie and Bell, 1971) and prolactin plays a part in its duration by affecting gonadotropin secretion and/or ovarian responsiveness to gonadotropins (Kutzler, 2005).

Administration of dopamine agonists shortens the duration of anestrus (Okkens et al., 1985; Van Haaften et al., 1989) and induces estrus in cases of prolonged anestrus (Arbeiter et al., 1988; Jochle et al., 1989). These ergot derivatives act by inhibiting prolactin secretion either by directly stimulating secretion of dopamine or by indirectly suppressing secretion of serotonine (Jochle et al., 1989; Beijerink et al., 2003). Low doses of bromocriptine (5µg/kg), however, have no significant influence on prolactin concentrations, but also significantly shorten the

interestrus interval (Beijerink et al., 2003) implicating that lowering prolactin concentrations is not the only mode of action.

Although some data are already available, there are significant differences between studies performed and sometimes also controversial results so that many questions are still open. So the aim of our study was to contribute to the knowledge about the effectiveness of the dopamine agonist bromocriptine for estrus induction in bitches.

MATERIALS AND METHODS

23 bitches of 14 different breeds (English pointer-2, English cocker spaniel-1, Samoyed-3, Chow chow-2, Pug-1, German hunting terrier-2, Cane corso-4, Kurzhaar-1, Bulgarian hunting dog-1, East siberian laika-1, Pomeranian-1, Bullterrier-2, American cocker spaniel-1 and Golden retriever-1) aged 2-6 years were presented at the Small animal clinic of the Faculty of Veterinary medicine, Trakia university, Stara Zagora, Bulgaria for estrus induction for various reasons. All animals were clinically and reproductively healthy. At the start of the treatment they were in anestrus (3-5 months after the last estrus) as confirmed by vaginal cytology and serum progesterone levels below 1 ng/ml.

Animals were treated initially with a daily dose of 0.025 mg/kg/d bromocriptine (Bromocriptine®, Sopharma, Bulgaria) orally for three days, followed by larger doses of 0.05 mg/kg/d for the same time period and then 0.1 mg/kg/d until day 5 of induced proestrus. The daily dose was divided into two and given by the owners in the morning and evening immediately after feeding.

Onset of proestrus was diagnosed by vulvar swelling and discharge and timing of fertile period was done using vaginal smears (Haemacolor®, Merck KGaA) and measuring of serum progesterone levels (HUMAN, PROG ELISA, GmBh, Germany). Ovulation was defined to be occurred at progesterone concentrations between 4 to 10 ng/ml.

Bitches were naturally bred twice with a male dog (from the same breed) on the 1st and 3rd day after ovulation. Pregnancy was diagnosed by use of an ultrasound scanner Mindray DC - 6 Vet and a 6.5 MHz transducer and printer Mitsubishi P91 E. At the time of parturition the litter size was documented.

RESULTS

Estrus induction

The results of estrus induction are summarized in Table 1.

Estrus occured in 22 of 23 bitches (96.65%). The period between treatment and onset of proestrus varied between 4 and 49 days, with an average of 22.86±12.34 days. Compared to spontaneous estrus no differences of the induced estrus were observed in regards of its duration, vaginal discharge and estrus symptoms. Ovulation was determined in 100% (22/22) of animals between 10th and 13th day after the onset of proestrus (11.1±0.99 days) as indicated by progesterone blood concentrations. Following matings, 19 bitches (86.35%) had normal pregnancy and parturition and litter size ranged between 2 and 11 puppies (5.00±2.36). Ultrasound examination showed that the other three bitches (13.75%) were not pregnant, but also no pathological findings in their reproductive organs could be identified for pregnancy failure. These three bitches, however, were successfully mated at their next spontaneous estrus period and had normal pregnancy and parturition.

One bitch (4.35%) did not respond to treatment at all as no signs of proestrus occurred until 56 days of treatment. The next estrus was observed 28 days after the termination of bromocriptine treatment. The bitch was mated in that estrus, got pregnant and gave birth to 8 live puppies.

Side effects

Two bitches had vomiting as a side effect of bromocriptine treatment when it started at high doses for 2-3 days. Afterwards and in none of the other bitches, further side effects were observed. The bitches affected by vomitus had normal estrus, pregnancy and both gave birth normally. A transient coat color change was observed in one black colored bitch that developed a grey fur until three weeks after the treatment was ceased.

Table 1. Induction of estrus in bitches with the dopamine agonist bromocriptine.

№ of bitches (n)	Proestrus,%/ Estrus,% (n)	Ovulation, % (n)	Pregnant, % (n)	Whelped, % (n)	Litter size (n)
23	**95.65%** (22/23)	**100%** (22/22)	**86.35%** (19/22)	**86.35%** (19/22)	**5±2.36**

DISCUSSION

Despite the population of bitches subjected to bromocriptine treatment was heterogeneus regarding breed, age and duration of treatment our results confirm previous studies that induction of fertile estrus and shortened interestrus intervals in a bitch can be successfully achieved with the dopamine agonist bromocriptine.

Reported results for estrus induction in bitches by bromocriptine treatment vary between 80% (Concannon, 1993; Concanon and Verstegen, 1997) and 100% (Van Haaften et al., 1989; Okkens et al., 1997; Zoldag et al., 2001; Beijering et al., 2003) and fertilization rates range between 60% (Van Haaften et al., 1989) and 83% (Zoldag et al., 2001). Our results are similar in good agreement with previous results. They also clearly show that all the animals with observable estrus symptoms ovulated and the fertilization rates are even higher (86.35%). Estrus did not occur in one animal only during treatment, but shortly after treatment. Consequently, it can just be speculated whether there is a correlation between bromocriptine treatment and the early start of estrus shortly after ceasing of treatment, most likely due to sensitization of its hypothalamus-pituitary axis, or not.

The variation in interestrus interval length owes itself to differences in the duration of anestrus which differs between and within dog breeds indicating a genetic basis for anestrus length (Okkens and Kooistra, 2006). Bitches with longer than average interestrus intervals have reduced opportunities to become pregnant (Chakraborty et al., 1982). But also to short interestrus intervals have an impact on fertility as it has been proven that histological changes in the endometrium of the bitches similar to involution are not complete until 135 days after the last estrus despite the bitch was pregnant or not (Anderson and Simpson, 1973). Therefore, induction of estrus before this time may result in reduced fertility and is not recommended.

In the past it was believed that inhibition of prolactin secretion using dopamine agonists was responsible for estrus induction in the bitch, as non-responders also fail to have a prolactin decrease (Concannon, 1993). It is also interesting to mention that in normal cycling bitches prolactin concentrations during late anestrus do not change prior to the onset of proestrus (Olson et al., 1982). Beijering et al. (2003) determined that administration of low doses of bromocriptine which do not lower plasma prolactin concentrations also shortens the duration of interestrus interval. This demonstrates that the mode of action of bromocriptine for estrus induction must be a different one that has not been identified yet.

Kooistra et al. (1999) determined that estrus induction by bromocriptine treatment was associated with an increase in plasma FSH concentrations without increasing in plasma LH concentrations, a situation also occurring physiologically in late anestrus (Okkens and Kooistra, 2006), when hypothalamus-pituitary axis affects ovarian steroidogenesis (Gobello, 2006).

CONCLUSION

The use of bromocriptine in the mentioned dosage protocol presents a reliable and cheap option for estrus induction in the bitch with a minimum risk for side effects and high chances for successful establishment of pregnancy.

CONFLICT OF INTEREST

None of authors is related either directly or indirectly to manufacturers of drugs and equipment mentioned in the present report.

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