The Pharma Innovation Journal 2019; 8(3): 375-377

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2019; 8(3): 375-377

www.thepharmajournal.com
Received: 04-01-2019
Accepted: 06-02-2019

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Shortening of Interoestrous interval (IEI) in dogs using low dose Cabergoline at early Anoestrus

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Abstract
Dopamine agonists have been successful in inducing oestrus in dogs with primary and secondary anoestrus. The present study assessed the efficiency and safety of dopamine agonist, cabergoline at a low dose during early anoestrous stage in reducing the IEI in dogs. Seventeen healthy dogs that completed 90 ± 3 days following the previous proestrus were randomly allotted to treatment and control groups. Cabergoline @ 0.6µg/kg b.wt/day orally was given until onset of proestrus or until day 40, if no signs of proestrus were observed. All the treated dogs evinced proestrual bleeding within a mean period of 23.83 ± 4.21 days of start of treatment. A significant shortening of IEI (120.17±15.89 days) and a satisfactory conception rate (66.67%) was noticed in the induced dogs.

Keywords: Dopamine agonist, primary anoestrus, secondary anoestrus, cabergoline and interoestrous interval

Introduction
Oestrous cycle is unique among dogs in that there is a non-seasonal anoestrus of a variable duration (2–10 months) following each oestrous cycle (Bouchard *et al*., 1991) [1]. Normal IEI in bitches ranges from 5 to 12 months and averages approximately 7 months. The interval varies greatly among bitches within the same breed. This highly unpredictable period of obligatory anoestrus decreases the benefits of a commercial dog
breeding programme. The factors regulating termination of anoestrus and the onset of a new oestrous cycle are not completely understood. However the termination of anoestrus happens with increased gonadotropin secretion or increased sensitivity to GnRH (Verstegen *et al*., 1999) [2]. Feldman and Nelson (1996) [3] reported that ninety days could be arbitrarily considered to be the duration of both follicular and luteal phases in dogs. Prolactin appears to play a role in the canine interoestrous interval, possibly by affecting gonadotropin secretion and ovarian responsiveness to gonadotropins (Beijerink *et al*., 2004) [4]. Though administration of dopamine agonists like bromocryptine, metergoline and cabergoline were reported to terminate an abnormally prolonged anoestrus in normal ovarian cycles of dogs, its efficiency in terminating the obligatory anoestrus in normal ovarian cycles of dogs are scarce. The present study was hence undertaken to assess the efficiency and reliability of dopamine agonist, cabergoline at low doses in inducing fertile oestrus during the early anoestrous stage of the normal ovarian cycle in dogs.

Materials and Methods
The study was conducted at University Veterinary Hospital, Kokkalai Thrissur, KVASU for a nine month period from August 2017 to May 2018.Seventeen healthy dogs of medium sized breeds aged 2 to 6 years, that completed 90 ± 3 days following the preceeding proestrus were selected. Anoestrous phase of the oestrous cycle was confirmed based on absence of intermediate and superficial cells in vaginal smears further confirmed by a serum progesterone level less than 1ng/ml. These dogs were randomly alloted to treatment (GI) and control groups (GII). Serum progesterone (P4) and prolactin (PRL) were analysed before and after treatment by ELFA (Enzyme Linked Fluroscent Assay) technique. Dogs in the treatment group was provided with cabergoline @ 0.6µg/kg bodyweight / day orally until onset of proestrus or until day 40 if no signs of proestrus were observed. Dogs in the control group as well as non responsive dogs in the treatment group were observed for signs of proestrus during the nine month study period. Breeding was adviced for dogs that evinced proestrual bleeding based on exfoliative vaginal cytology (EVC), vaginoscopy and serum progesterone assay and breeding was done with healthy proven fertile male dogs.

Oestrous response rate, conception rate, gestation length, gestational accidents, and whelping rate were evaluated during the period of study. The data were statistically analysed using SPSS 24.0 version.

Results and Discussion

The overall mean (±SE) interval from the last proestrual bleeding to initiation of treatment was 91.18±0.55 d with a range of 87 to 93 d. As per the haematological parameters and BCS, all selected animals were found to be healthy. The mean (±SE) progesterone (P4) level (ng/ml) in GI and GII was 0.71 ±0.07 and 0.30±0.07 respectively and EVC revealed parabasal cells and small intermediates assuring that all animals were in anoestrous phase of the oestrous cycle. According to Sirivaidyapong (2011) [5] female dogs with progesterone level below 1 ng/ ml could be deemed to be in anoestrus. The mean serum prolactin level (ng/ml)) in selected animals before treatment was <0.5 in both GI and GII. This indicates the nonexistence of any hyperprolactinaemia in both treatment and control groups. Verstegen *et al*.(1999) [2] observed that serum prolactin concentrations in dogs at mid anoestrus was 1.6 ± 0.8 ng/ml and did not vary significantly in early, mid and late anoestrous. The decreased prolactin level noticed in this study when compared to study by Verstegen *et al* (1999) [2] could be attributable to the difference in assay methods employed.

The response to cabergoline administration in dogs of GI at 91.18±0.55 days of preceding proestrus was Cent percent as evinced by the display of proestrual bleeding by all the dogs. The mean duration from initiation of treatment to exhibition of proestrual bleeding was 23.83 ± 4.21 d. In the control group, only 6 animals (54.55%) exhibited oestrus throughout the nine month period of study. Mean (±SE) duration of proestrus in treated group (GI) was 9.67 ± 0.96 d and 10.45 ± 0.71 d in the control. Mean (±SE) duration of oestrus in GI was 7.67 ± 0.42 and 7.55 ± 0.41 d in control group. Average duration of proestrus and oestrus noticed correlates with the findings of earlier study by Cirit *et al*. (2007) [6] who did not observe any difference in the duration of proestrus and oestrus in cabergoline induced and normally cycling dogs.

The behavioural characters such as intensity of proestrual bleeding, intensity of vulval oedema, interest towards male and tail deviation reflex in the induced oestrus were similar to spontaneous oestrous cycles. The mean (±SE) serum progesterone concentration (ng/ml) in GI and GII were 1.69 ± 0.10 and 1.87 ± 0.09 during proestrus, 4.92 ± 0.54 and 4.50 ± 0.38 during oestrus and increased to 16.76 ± 0.85 and 16.65 ± 0.55 during metoestrus. No significant difference in serum progesterone concentration during proestrus, oestrus, and metoestrus was noticed between the dogs of induced and natural oestrus. Similar observations in serum progesterone concentration during proestrus, oestrus and metoestrus have also been reported by Sreedevi and Veerapandian (2011) [7]. No detectable difference in the serum prolactin level (<0.5 ng/ml) was observed before and after treatment in cabergoline treated dogs as well as in control animals. Similarily no dissimilarity in the Anuclear Cell Index (ACI) was noticed between treated and control dogs both during proestrus and oestrus. The vaginoscopic appearance of vaginal mucosa during proestrus and oestrus did not fluctuate between the groups. The non-varriance of hormonal, cytological and vaginal mucosal characteristics between the induced and spontaneous oestrus signifies that cabergoline could induce a normal oestrus and ovulation.

A decrease in interoestrous interval (120.17 ± 15.89 d) was recorded in cabergoline treated dogs (114.83 ± 4.59 d) in comparison to its preceding interoestrous interval (235.00 ± 18.03 d). However, in control dogs, an elongation of interoestrous interval by 56.50 ±9.18 d was noticed (228.00 ±15.47 against 171.67 ± 13.90). The reduction in IEI in treatment dogs was significantly variable from the control dogs ($p<0.05$). The termination of anoestrus with cabergoline in the present study was not related to effect on prolactin and progesterone as both the hormones were lower at the start of treatment. Kooistra and Okkens (2002) [8] also reported that canine anoestrus was charecterised by low plasma prolactin levels and there is no precise change in plasma prolactin level during the intiation of a follicular phase following the termination of anoestrus. Similarly Spattini *et al*. (2007)[9] observed an increase in LH concentration without an effect on plasma prolactin level on administration of cabergoline in anoestrous bitches.The successful response to low dose cabergoline could be attributed to the observations of Spattini *et al*. (2007) [9] who reported an increase in LH concentration without an effect on plasma prolactin level on administration of cabergoline in anoestrous dogs.

Conception rate among the animals that exhibited oestrus following treatment and without treatment (control) was 66.67 per cent (4/6) during the 9 month period of study. Gestation length in treatment and control group was without difference (61.25±0.63 and 60.25±0.90 days). Average litter size in treatment group was 6.25±1.75 and in control group, it was 4.56±0.42. The neonatal survival rate in treatment and control group was 100 and 84.90 per cent. No side effects like vomiting, nausea and anorexia was noticed in cabergoline treated animals when the drug was provided before food.

The induced oestrous cycle in cabergoline treated animals was identical to natural oestrous cycle, based on vaginal cytology and evidence of ovulation. Duration and physical characteristics were also similar to natural oestrous cycle in control group. The present study hence, confirmed the efficiency of 0.6µg/kg b. wt cabergoline in shortening the IEI in dogs when administered during early anoestrus stage. A normal oestrus and fertile ovulation was also assured as evident by normal duration of proestrus and oestrus with a satisfactory conception rate following breeding in induced oestrus.

Table 1: Comparison of the efficacy of low dose cabergoline treatment with control group

Sl. no.	Parameters	Treatment group (GI)	Control group (GII)
1.	Serum P4(ng/ml)	0.71 ±0.07	0.30 ±0.07b
2.	Serum PRL(ng/ml)	<0.5	<0.5
3.	Treatment duration (d)	23.83 ± 4.21	NA
4.	Oestrous response rate (%)	100a	54.5b
5.	Duration of proestrus (d)	9.67±0.96	10.45±0.71
6.	Duration of oestrus (d)	7.67±0.42	7.55±0.41
7.	Reduction of IEI (d)	120.17± 15.89a	-56.50 ±9.18b
8.	Conception rate (n)	66.67%(4/6)	66.67%(4/6)
9.	Whelping rate (n)	66.67% (4/6)	66.67%(4/6)

Means with different superscripts differs significantly ($p<0.05$)
NA - not applicable

Acknowledgement

The authors are thankful to the Dean, College of Veterinary and Animal Sciences, Mannuthy for providing the facility for the conduct of the study.

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