Journal of Animal and Veterinary Advances 9 (12): 1735-1738, 2010
ISSN: 1680-5593

Comparative Efficacy of High vs. Low Dose Cabergoline Treatment Regimen in Inducing Fertile Oestrus in Anoestrous Dogs

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Abstract: Twenty four bitches in anoestrus for >6 months from the last heat with a serum progesterone level >1 ng mL^{-1} were divided into two groups and subjected to oestrus induction trials using anti-prolactin drug cabergoline at 5 and 1 μg kg^{-1} body weight respectively, once daily orally for 20 consecutive days. The mean serum progesterone level among them during anoestrus was found to be 0.56±0.01 ng mL^{-1}. Out of 12 animals treated in each group, 10 (83.34%) in group I and 9 (75%) in group II responded by evincing proestrual bleeding. The mean (±SEM) time taken from initiation of treatment to onset of proestrual bleeding in Groups I and II was 13.50±0.50 ($p<0.01$) and 21.89±0.86 days, respectively. About 25% of animals treated with high dose cabergoline exhibited side effects as against none with low dose. The mean (±SEM) duration of proestrus and oestrus in the treatment groups was 8.70±0.30 ($p<0.05$) and 9.56±0.38 days and 8.20±0.29 and 8.33±0.24 days, respectively. The conception rate in relation to the number of animals responding to oestrus induction in the treatment groups was 90 and 88.89%, respectively. The mean (±SEM) gestation length calculated from the last breeding date and litter size in the treatment groups were 62±0.41 and 62.88±0.49, 6.44±0.29 and 6.13±0.23, respectively.

Key words: Bitch, infertility, anoestrus, oestrus induction, cabergoline, conception rate

INTRODUCTION

The oestrous cycle in the bitch is considerably longer than that in most other domestic species and unique in that there is an obligatory anoestrus following the termination of the luteal phase. Bouchard *et al.* (1991) and Concannon (1993) reported a non-seasonal anoestrus of variable duration (2-10 months) following each oestrous cycle in bitch. According to Feldman and Nelson (1996), anoestrus could be primary (the bitch that never had an ovarian cycle) or secondary (the bitch that had one or more ovarian cycles but subsequently failed to cycle) and it was opined that secondary anoestrus could occur after the onset of endocrine or non-endocrine diseases.

Prolactin appears to play a part in canine interoestrus interval, possibly by affecting gonadotrophin secretion and/or ovarian responsiveness to gonadotrophins. Dopamine is the main endogenous factor inhibiting the release of prolactin and for this reason it is often defined as the prolactin inhibitory factor (Cortese *et al.*, 1997). Suppression of prolactin secretion by administration of dopamine agonists shortened the duration of anoestrus (Van Haaften *et al.*, 1989) and induced oestrus in cases of prolonged anoestrus (Arbeiter *et al.*, 1988; Jochle *et al.*, 1987). Davidson (2006) suggested that prolactin secretion by the pituitary might promote anoestrus and hence dopamine agonists such as cabergoline and bromocriptine could be used to shorten anoestrus in both the normal bitch and in bitches with secondary anoestrus of unknown etiology.

Jochle *et al.* (1987) and Harvey *et al.* (1997) reported that cabergoline has a more specific action on D2 dopamine receptors of the anterior pituitary gland and therefore has a greater activity and long lasting effect than bromocriptine. Arbeiter *et al.* (1988) reported development of tolerance to cabergoline with continued therapy and found lesser degree of side effects with lower

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dose. Del Dotto and Bonucelli (2003) reported that cabergoline could be administered once daily which was advantageous over other dopaminergic agents in terms of both therapeutic compliance and better symptom control. Review of literature revealed reports of induction of fertile oestrus in anoestrous bitches using cabergoline at 5 μg kg^{-1} body weight or higher doses (Ajitkumar *et al*., 2010; Gobello *et al*., 2001, 2002; Jeukenne and Verstegen, 1997; Jochle *et al*., 1987; Rota *et al*., 2003). On the other hand Cirit *et al*. (2007) reported successful induction of normal oestrus and ovulation in breeder bitches with a low dose of 0.6 μg kg^{-1} body weight day^{-1} of cabergoline. In earlier oestrus induction trials with high dose cabergoline, some side effects such as vomiting had been reported in 10-25% of dogs (Arbeiter *et al*., 1988; Gobello *et al*., 2001; Gunay *et al*., 2004; Dattatray, 2006). However, Arbeiter *et al*. (1988) and Cirit *et al*. (2007) reported lesser degree of side effects with lower dose of cabergoline.

Popularization of the nuclear family concept and the day to day changes happening in the socio-cultural scenario make dog as an important member of the family in developing countries too. Even though dog is considered primarily as a pet and companion, many have identified the potential of dog breeding units as a remunerative vocation. Here comes the importance of timely reproduction in making dog breeding units viable and profitable. Now a days many owners are approaching veterinarians with the complaint of anoestrus in their bitches. Though, literature revealed the successful induction of fertile oestrus in bitches using cabergoline at 5 μg kg^{-1} body weight, there is paucity of data comparing the effect of high versus low dose treatment regimen on induction of fertile oestrus and the side effects. Hence a study was undertaken to compare the efficacy of cabergoline treatment at two dose rates in inducing fertile oestrus in anoestrous bitches.

MATERIALS AND METHODS

Privately owned female dogs of various breeds brought to the Gynaecology Unit of University Teaching Veterinary Hospital, Kokkalai, Thrissur, Kerala, India with the history of anoestrus for a minimum period of 6 months from the last whelping date were subjected to exfoliative vaginal cytology to ascertain the stage of the oestrous cycle. Those bitches which were found to be in anoestrus on cytology were further subjected to serum progesterone estimation for confirmation and from among them, 24 apparently healthy animals aged between 1.5-4 years with serum progesterone level <1 ng mL^{-1} were selected at random and divided in to two equal groups viz. I and II. The animals in group I and II were administered with cabergoline at 5 μg kg^{-1} body weight and 1 μg kg^{-1} body weight, respectively once daily orally for 20 consecutive days. In order to minimize the side effects, the owners were advised to administer the drug along with food. Those bitches which responded to the treatment by evincing proestrual bleeding were subjected to exfoliative vaginal cytology to identify the best time for breeding based on anuclear cell index and were bred with apparently healthy, fertile male dogs repeatedly at 72 h interval until refusal of the male. In order to rule out silent heat among those bitches which failed to exhibit proestrual bleeding, serum progesterone concentration was again estimated one month after the completion of treatment. Transabdominal ultrasonography (B-mode, 3.5 MHz sector probes) and abdominal palpation were used for pregnancy diagnosis between 20 and 25 days and 30 and 35 days post-breeding, respectively. All the bitches found pregnant were followed up periodically until whelping and the details pertaining to gestation length and litter size were collected. The data obtained were compiled and subjected to Student's t-test to find out statistically significant difference between the groups (Snedecor and Cochan, 1989).

RESULTS AND DISCUSSION

An investigation carried out to compare the efficacy of high vs. low dose cabergoline treatment regimen in inducing fertile oestrus revealed that the serum progesterone level in anoestrous bitches ranged from 0.45-0.65 ng mL^{-1} with a mean (±SEM) of 0.56±0.01 ng mL^{-1}. Out of the 12 animals treated in each group, 10 in group I (83.34%) and 9 in group II (75%) evinced proestrual bleeding. The mean (±SEM) serum progesterone level among bitches failed to exhibit proestrual bleeding was 0.59±0.03 ng mL^{-1}.

The mean (±SEM) serum progesterone level of 0.56±0.01 ng mL^{-1} noticed among the bitches selected for the oestrus induction trials confirmed that all of them were in the anoestrus stage at the time of the treatment. On induction of oestrus using cabergoline, the proestrus response was found to be higher (83.34%) at a dose rate of 5 μg than 1 μg kg^{-1} body weight (75%). On administration of cabergoline at the rate of 5 μg kg^{-1} body weight once daily orally in anoestrous bitches, Verstegen *et al*. (1999) and Ajitkumar *et al*. (2010) could obtain 93.33 and 90% proestrus response, respectively. Even though Cirit *et al*. (2007) could obtain a higher (81.50%) proestrus response on treatment with cabergoline at the rate of 0.6 μg kg^{-1} body weight daily than with 5 μg (80%) in the present study it was found to be higher on treating with high dose than with low dose

cabergoline. The mean (±SEM) serum progesterone level of 0.59±0.03 ng mL^{-1}, noticed among bitches failed to exhibit proestrual bleeding on induction of oestrus, ruled out the occurrence of silent oestrus and that all of them continued in the anoestrous stage.

The mean (±SEM) time taken from initiation of treatment to onset of proestrual bleeding in the two treatment groups was 13.50±0.50 ($p<0.01$) and 21.89±0.86 days respectively. The mean (±SEM) duration of proestrus and oestrus based on cytology in the treatment groups was 8.70±0.30 ($p<0.05$) and 9.56±0.38 days and 8.20±0.29 and 8.33±0.24 days, respectively. Out of 12 animals treated with high dose of cabergoline, 3 (25%) exhibited nausea, vomiting and inappetance as side effects of treatment. On the other hand, none in the group treated with low dose exhibited the above mentioned side effects.

The mean (±SEM) time taken from the treatment onset to proestrus in animals induced with cabergoline at the rate of 5 μg kg^{-1} body weight (Group I) was found to be significantly lower ($p<0.01$) than that in group II (13.50±0.50 vs. 21.89±0.86 days). Gobello *et al.* (2002) successfully induced oestrus in anoestrous purebred bitches by administering cabergoline at the rate of 5 μg kg^{-1} body weight orally and according to them, the mean duration of treatment required was 16 days. From the results of the present study, it could be inferred that low dose cabergoline treatment regimen takes more days for inducing oestrus than high dose regimen. Even though the duration of proestrus in group I was found to be significantly ($p<0.05$) lower than that in group II, the duration of proestrus and oestrus in the induced cycles in both the groups was found to be within the normal range and was in agreement with the previous reports (Jeukenne and Verstegen, 1997; Verstegen *et al.*, 1999; Gobello *et al.*, 2004).

In earlier oestrus induction trials with cabergoline, some side effects such as vomiting had been reported in 10-25% of dogs (Arbeiter *et al.*, 1988; Gobello *et al.*, 2001; Gunay *et al.*, 2004; Dattatray, 2006). In the present study, even though the drug was administered along with food, 25% of animals treated with high dose cabergoline exhibited side effects as against none treated with low dose. This observation is in consonance with the earlier reports of Arbeiter *et al.* (1988) and Cirit *et al.* (2007) who found lesser degree of side effects with lower dose of cabergoline.

The accuracy of pregnancy diagnosis by transabdominal ultrasound scanning increased from 88.23-100% when performed between 20, 25 days and 30, 35 days post-breeding and the corresponding values for abdominal palpation were 76.47 and 94.12%, respectively. Out of 10 and 9 animals in group I and II which responded to the oestrus induction treatment 9 and 8, respectively conceived and subsequently whelped uneventfully. The conception rate in relation to the number of bitches responding to the oestrus induction treatment in the two treatment groups were 90 and 88.89%, respectively. The conception rate obtained with high dose in the present study was found to be better than that of Rota *et al.* (2003) and Gobello *et al.* (2004) who reported 83 and 82.60% conception rate respectively on oestrus induction using cabergoline at the rate of 5 μg kg^{-1} body weight.

The mean (±SEM) gestation length calculated from the last breeding date and the litter size in the treatment groups were 62±0.41 and 62.88±0.49 days and 6.44±0.29 and 6.13±0.23, respectively. With respect to gestation length and litter size, significant difference could not be detected between the treatment groups.

CONCLUSION

Oestrus induction trials carried out to compare the efficacy of cabergoline treatment at high and low dose rates in anoestrous bitches revealed that the proestrus response and conception rate were better with the high dose regimen which took fewer days for induction but with side effects in 25% of animals treated.

On the other hand, even though the low dose regimen took more days for induction with slightly lower proestrus response and conception rate, none of the animals in this group exhibited side effects. From the present investigation, it could be concluded that even though the high dose cabergoline treatment regimen recorded earlier induction of oestrus with better proestrus response and conception rate, the lower dose regimen was found to be safe with moderate results.

ACKNOWLEDGEMENTS

Thanks are due to the Professor and Head, University Veterinary Hospital, Kokkalai for the facilities provided and the Dean, Faculty of Veterinary and Animal Sciences, Kerala Agricultural University for granting permission to publish this study.

REFERENCES

Ajitkumar, G., T. Sreekumaran, R. Praseeda, K.A. Mercy and K.N.A. Ghosh, 2010. Comparative efficacy of bromocriptine, cabergoline and thyroxine in inducing oestrus in bitches. Vet. Res. Commun., 34: 65-69.

Arbeiter, K., W. Brass, R. Ballabio and W. Jochle, 1988. Treatment of pseudopregnancy in the bitches with cabergoline-an ergoline derivative. J. Small Anim. Practice, 29: 781-788.

Bouchard, G.F., R.S. Youngquist, D. Vaillancourt, G.F. Krause, P. Gunay and M. Paradis, 1991. Seasonality and variability of the inter-oestrous interval in the bitch. Theriogenology, 36: 41-50.

Cirit, U., S. Bacinoglu, I.T. Cangul, H.H. Kaya, M. Tas and K. Ak, 2007. The effects of a low dose of cabergoline on induction of oestrus and pregnancy rates in anoestrous bitches. Anim. Reprod. Sci., 101: 134-144.

Concannon, P.W., 1993. Biology of gondotrophin secretion in adult and prepubertal female dogs. J. Reprod. Fertil. Suppl., 47: 3-27.

Cortese, L., G. Oliva, J. Verstegen, P. Ciaramella and A. Persechino, 1997. Hyperprolactinaemia and associated galactorrhoea associated with primary hypothyroidism in a bitch. J. Small Anim. Practice, 38: 572-575.

Dattatray, P.M., 2006. Induction of oestrus in bitches using dopamine agonist. M.Sc. Thesis, Tamilnadu Veterinary and Animal Sciences University, Chennai, pp: 62.

Davidson, A., 2006. Current concepts on infertility in the bitch. Focus, 16: 13-21.

Del Dotto, P. and U. Bonucelli, 2003. Clinical pharmacokinetics of cabergoline. Clin. Pharmacokinet., 42: 633-645.

Feldman, E.C. and R.W. Nelson, 1996. Ovarian Cycle and Vaginal Cytology. 2nd Edn., W.B. Saunders Co., Philadelphia, pp: 526-545.

Gobello, C., F. Bolognani, R.D.L. Sota and R. Gaya, 2001. Twenty four hour profiles of serum prolactin and luteinising hormone in anoestrous crossbred bitches. Reprod. Domest. Anim., 36: 41-45.

Gobello, C., G. Castex and Y. Corrada, 2002. Use of cabergoline to treat primary and secondary anoestrus in dogs. J. Am. Vet. Med. Assoc., 220: 1653-1654.

Gobello, C., G. Castex, R.D.L. Sota and Y. Corrada, 2004. Shortening of interoestrous intervals with cabergoline in bitches: A clinical trial. J. Am. Anim. Hospital Assoc., 40: 115-119.

Gunay, A., U. Gunay and M.K. Soylee, 2004. Cabergoline applications in early and late anoestrous periods on German shepherd dogs. Revue Med. Vet., 155: 557-560.

Harvey, M.J.A., A. Cauvin, M. Dale, S. Lindley and R. Ballabio, 1997. Effects and mechanism of the anti-prolactin drug cabergoline on pseudopregnancy in the bitch. J. Small Anim. Practice, 38: 336-339.

Jeukenne, P. and J. Verstegen, 1997. Termination of dioestrus and induction of oestrus in dioestrus non-pregnant bitches by the prolactin antagonist cabergoline. J. Reprod. Fertil. Suppl., 51: 59-66.

Jochle, W., R. Ballabio and E. Disalle, 1987. Inhibition of lactation in the Beagle bitch with the prolcatin inhibitor cabergoline (FCE 21336): Dose response and aspects of long term safety. Theriogenology, 27: 799-810.

Rota, A., A. Mollo, L. Marinelli, G. Gabai and L. Vincenti, 2003. Evaluation of cabergoline and buserelin efficacy for oestrous induction in the bitch. Reprod. Domest. Anim., 38: 440-443.

Snedecor, G.W. and W.G. Cochan, 1989. Statistical Methods. 8th Edn., Iowa State University Press, Ames, IA., pp: 503.

Van Haaften, B., S.J. Dieleman, A.C. Okkens, M.M. Bevers and A.H. Willemse, 1989. Induction of oestrus and ovulation in dogs by treatment with PMSG and/or bromocryptine. J. Reprod. Fertil. Suppl., 39: 330-331.

Verstegen, J.P., K. Onclin, L.D.M. Silva and P.W. Concannon, 1999. Effect of stage of anoestrus on the induction of oestrus by the dopamine agonist cabergoline in dogs. Theriogenology, 51: 597-611.