

The Utilization Areas of Cabergoline in Veterinary Gynecology

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Abstract

Cabergoline is a potent dopamine agonist and a synthetic ergot derivative, and it acts by inhibiting prolactin secretion from the pituitary gland. It reduces the amount of plasma prolactin and inhibits progesterone secretion at the same time. Because of these effects, it has found a widespread area of use in the treatment of hyperprolactinemic disorders both in the human medicine and veterinary medicine.

Keywords: cabergoline, veterinary, gynaecology

Introduction

Prolactin is a hormone in the polypeptide structure that is secreted from specific lactotroph cells in the adenohypophysis. The main function of the prolactin is the onset and continuation of lactation; however, numerous of its tasks have been reported both inside and outside the reproductive system. The secretion of prolactin is under control of tonic inhibition of prolactin inhibitory factors. The most important prolactin inhibitory factor is dopamine. Dopamine inhibits adenylate cyclase by binding to the dopamine D2 receptors on lactotroph membranes and reduces the prolactin release. In this review, indications of cabergoline in veterinary gynaecology were evaluated by a clinician. It is aimed to draw attention to the importance of cabergoline and to shed light on the works that can be planned in the future.

Cabergoline

Cabergoline (CAB) (1-[(6-allyl)ergolin-8 b-yl)carbon-

yl]-1-[3-(dimethylamino)propyl]-3-ethyl-urea) is a potent dopamine-2 (D2) receptor stimulant and synthetic ergot derivative. It creates an effect by inhibiting the prolactin secretion from the pituitary gland.^{1,2}

Cabergoline is the newest dopamine agonist used in the treatment of hyperprolactinemic disorders both in human and veterinary medicine. The inhibition of prolactin secretion occurs via dopamine. Cabergoline has high selectivity and affinity against the dopamine D2 receptors that are in pituitary prolactin secreting cells and acts through these receptors.^{3,4} Cabergoline inhibits prolactin secretion in vivo and in vitro pathways and constitutes a stronger prolactin inhibition than other dopamine agonists. It has been reported in the studies carried out on rats that the treatment of single-dose 0.6 µg/kg CAB reduce the concentrations of prolactin for 6 days, and the CAB application inhibits the progesterone secretion in pregnant cats and dogs.³⁻⁷

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Estrus Induction in Bitches

Bitches are monoestrus type animals that are not dependent on the season. In general, they reach puberty at 6-14 months of age. The time between two standing heats is 7 months on average and varies between 5-12 months.^{8,9} The bitches enter the anestrus period after the diestrus period of the cycle. The anoestrus period is long and approximately 120 (40-270) days. Duration of this time may vary depending on the races and the individuals.¹⁰ The prolongation of the anestrus period is an infertility cause and is divided into two categories as the primary and secondary anestrus. The primary anestrus is the state that the female dog does not have any estrus until 24 months of age, and the secondary anestrus is the state that it does not have oestrus even though 10-18 months have passed after the previous estrus period.⁹

One of the drugs used in bitches for the termination of an anestrus to form estrus is CAB which is a dopamine agonist. Cabergoline is an ergot alkaloid and has an anti-prolactinergic effect.^{11,12} Suppression of prolactin secretion via dopamine agonists shortens the duration of anestrus and induces the estrus.¹³ It has been reported that the use of CAB in the treatment of both primary and secondary anestrus cases in dogs induces estrus and provides a high pregnancy rate. Cabergoline is recommended at 5 µg/kg doses to stimulate the estrus in dogs and reported to be effective also at low doses (0.6 µg/kg).¹⁴⁻¹⁷ Unlike dogs, CAB has not been shown to be effective in inducing estrus in cats.⁵

Termination of Pregnancy Dogs and Cats

In dogs, prolactin is the luteotropic hormone in the second half of the luteal phase. Prolactin provides the continuity of progesterone by supporting the corpus luteum. Cabergoline, which has an anti-prolactin effect, suppresses luteal functions, causing the decrease of the progesterone concentration and the termination of the pregnancy.^{6-18,19} Cabergoline is effective in the second half of pregnancy for the termination of the pregnancy in dogs, and it can be used to terminate advanced and middle term pregnancies.²⁰

Onclin et al.²¹ reported that the treatment of pregnant dogs between 25 and 40 days by subcutaneous injection of CAB for 5 days at 1.65 µg/kg dose displayed a 1/4 abortion at 25th day, 4/6 at 30th day and 5/5 at 40th day. Moreover, it was reported that the abortion was achieved by the oral use of 160 µg of CAB for 7 days after the 40th day of pregnancy and no side effects were observed.²² It has been reported that CAB can be used in combination with PGF2α analogues in abortion prophylaxis in dogs. This combina-

tion is effective from 25th day of the pregnancy in which is applied at 5 µg/kg orally for 9-10 days whereas 1 µg/kg subcutaneous cloprostenol is used at 28th and 32nd days of the pregnancy.²³

Because of the harmful side effects, the uses of estradiol and PGF2α has been reported to be unsafe in preventing pregnancy in cats, hence cabergoline and aglepristone are better tolerated.²⁴ Verstegen et al.⁶ indicates that there is no adverse effect or behavioural disturbance in the cats on the 30th day of gestation, at dose of 1.65 µg/kg subcutaneous injection of Cabergoline for five consecutive days and 80% abortion is available. Cabergoline is effective in termination of pregnancy in female cats between 34th and 42th days of pregnancy, when it is used alone, however the combination with PGF2α is more effective between 25th and 40nd days of pregnancy.²⁵

Cystic Endometrial Hyperplasia Pyometra Complex Treatment in Queen and Bitch

Cystic endometrial hyperplasia-pyometra complex (CEH-P) is a disease characterized by purulent fluid accumulation in uterine lumen, cystic dilatation and endometrial hyperplasia in endometrial gland. This case is often seen during the diestrus period, since the cycle is under effect of the influence of progesterone. The frequency of this disease in cats is lesser than those in dogs.²⁶

The most important luteotropic hormone in dogs is prolactin. Cabergoline is revealed to be inhibiting the action of prolactin and reducing the plasma progesterone concentration.²¹ In the medical treatment of CEH-P, CAB is used to reduce the serum progesterone concentration (luteolytic effect) and its combination with prostaglandins is recommended to relieve the uterine contents. England et al.²⁷ found that the combination of CAB-prostaglandin (5µg/kg of CAB once a day for 10 days, and 5µg/kg cloprostenol for 3 times SC. in 3 days intervals) decreased plasma progesterone concentration, increased vaginal secretion and reduced uterine diameter. Jena et al.²⁸ reported that the most effective treatment protocol for their studies comparing various treatment protocols in pyometra cases of dogs was using cloprostenol (1 µg/kg SC. 7 days) in combination with CAB (5 µg/kg oral 7 days).

It has been reported that the dopamin agonist CAB (5 µg/kg oral) can be used alone, combined with prostaglandins or combined with anti-progestins, a rapid luteolysis is provided by the combination of PGF2α and CAB and the cervix is opened in 24-48 hours, in pyometra cases of cats.²⁶

Pseudo-Pregnancy Treatment in Dogs

Pseudo-pregnancy (PSP) is a common syndrome characterized by nesting, gaining weight, growth in udders,

increasing milk secretion and maternal behaviour in non-pregnant dogs at the end of the metestrus stage. It may show subclinical or clinical courses. Although the exact physiopathology of the PSP is not fully understood, it has been determined that prolactin hormone levels increase, whereas progesterone hormone levels decrease and it occurs in 6-12 weeks after estrus.^{29,30}

Diuretics, progestagens, estrogen, and androgen combinations have been used in the medical treatment of pseudo-pregnancy, however, their usage is contraindicated due to the incidence and severity of side effects. Today, prolactin antagonists are effective in the treatment of symptoms within the next 10 days from the start of treatment.³¹ These drugs have been proven to decrease the level of prolactin, lower the serum levels and thus regress udder gland development, reducing pseudo-pregnancy behaviours.³² It was reported that, in the treatment of pseudo-pregnant dogs, application of daily 5 mg/kg, prolactin antagonist, CAB for 5 days was highly effective and no side effects were observed.³³⁻³⁵

Treatment of Mammary Hyperplasia in the Cats

In cats, fibroepithelial udder hyperplasia is a benign disease characterized by progesterone related sudden and rapid fibroglandular proliferation of one or more mammary glands.³⁶ It is reported that this is more common in young female cats but may be seen in male cats.³ This disease is often found in animals treated with progesterone or analogues. Progesterone antagonists (aglepristone) and prolactin inhibitors (cabergoline) can be used to treat the disease. Or ovariectomy may be recommended. Medical treatment of this disease is frequently recommended in cats especially that are breed for production.^{36-38, 39}

In mammary hyperplasia cases with milk secretion, it was reported that successful results were gained with the combined use of Aglepristone (two days a week for three weeks, at the dose of 15 µg/kg, subcutaneously) and CAB (at the dose of 5 µg/kg once a day per os, at the first week).⁴⁰

Utilization of Cabergoline in Drying Off the Dairy Cows

Dairy cows need a dry period between the two lactations to provide high milk yield.⁴¹ This period, in which the udders of the cows are rested between the two lactation periods and not milked for the last 45-60 days of the pregnancy, is called the dry period, and the process at the beginning of this period is called drying off. In order to dry the cows off from the milking, there are methods such as intermittent milking, not evacuating the milk in the udder completely or sudden cease of milking.⁴² In recent years, it has been reported that, as an alternative to conventional drying off methods, successful results have been obtained

with a single CAB injection in transition to the drying off phase.^{41-43,44} Cabergoline is a high-affinity ergot derivative for D2 dopamine receptors, whose dopaminergic effects cause the inhibition of prolactin secretion. Therefore, as a result of studies carried out considering CAB as a potential drying off molecule, it was concluded that the intramuscular injection of a single dose of 5.6 mg of CAB on the cows, which gives over 16 kg of milk in the transition to dry period, Cabergoline treatment positively influences dry period mammary health and reduces risk factors for animal welfare.⁴⁴

In similar studies, it was reported that the same dose of CAB facilitated the drying of the udder gland and udder gland involution, reduced prolactin release and leakage from the udder, and prolonged the resting time after the drying off.⁴¹⁻⁴³ Cabergoline treatment will be beneficial because it accelerates mammary involution and decreases milk secretion in the transition to dry period.

Conclusion

As a result, CAB has found a utilization area in veterinary gynaecology, especially in the medical treatment of various gynaecological disorders of carnivorous, and it is advantageous for it to have fewer side effects than other hormone drugs. However, it is not used in dairy cattle in our country as it is used in European countries. Since the CAB is thought to be useful as a medicine to increase the health and comfort of the cows to be dried off, to increase the number of the studies in this area and to use it in cattle in our country is deemed to be beneficial.

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