

Antiprogestin use in Europe



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Abstract

Aglepristone is a competitive progesterone antagonist that binds to progesterone receptors and is used in small animal reproductive management. This article is a brief review of the following aspects: approved use in pregnancy termination in bitches and queens; medical treatment of pyometra; induction of parturition; planning of an elective cesarean section; and treatment of feline mammary fibroadenomatosis.

Keywords: Aglepristone, antiprogestin, small animals, reproductive management

Introduction

Aglepristone is a competitive progesterone antagonist that binds to progesterone receptors and thereby impairs the biological effects of progesterone. It is an antiprogestin, with similar molecular structure to mifepristone used in human medicine. Its affinity to progesterone receptor is 3.12 and 9.26 times higher than progesterone for the bitch and queen, respectively.¹ An aglepristone progesterone compound (Alizin® [Virbac, France]) is approved in Europe as a subcutaneous (SC) injection. It is also available in Australia, New Zealand, Canada and in the US under a controlled use drug prescription. It is used in situations wherein the objective is to block the progesterone action (reviewed^{1,2}). Applications include, pregnancy termination in bitches (only approved indication) and queen, medical treatment of pyometra, induction of parturition, in deciding elective cesarean section (c-section), and treatment of feline mammary fibroadenomatosis.

Pregnancy termination

A case of 'misalliance' (unwanted mating) can be treated in 2 ways under the supervision of a licenced veterinarian. Either a dose of alizin® (10 mg/kg, SC) is given after end of estrus (confirmed by vaginal cytology) not knowing if the mating resulted in a pregnancy, or terminating pregnancy once confirmed by ultrasonography. In both cases, a second dose (24 hours later) is necessary. However, in our experience, a third dose (1 week after the first injection) is necessary for most pregnant dogs. Although the efficacy at the end of estrus is higher than 95%, it is worthwhile to examine for pregnancy.

Additionally, cases of pregnancy termination should be followed

(1 week later) by abdominal ultrasonography to ensure that pregnancy is arrested (no viable embryo/fetuses remaining) and evaluate the amount of fluid in the uterine lumen. Although the efficacy of the product is closer to 100%, in late pregnancy (> 38 days) it may require repeated treatment for total efficacy. Treatment failure is rare. Pregnancy termination (before 45 days) is the only indication for approved use. Therefore, alizin® use in pregnancies over 45 days is not recommended and is also 'off-label.' Side effects vary and seem to be associated with the onset of the treatment in relation to the stage of pregnancy. Following signs were observed: anorexia and/or depression (with weight loss), vomiting, diarrhea, and polydipsia. Vaginal discharge, if observed, started within 2 days after the onset of treatment and lasted 1 - 2 weeks in bitches that were at least 30 days pregnant. Its use in a late stage of pregnancy (~ 40 days) can lead to fetal expulsion. It must be noted that alizin® shortens the interestrus interval.

Terminating unwanted pregnancies in the queen with alizin® is 'off-label.' When used as early as days 5 - 6 after mating, the success was closer to 100%,³ termination rates decreased to ~ 88 % between days 25 - 35. The efficacy is as low as 67% in queens treated after 45 days of pregnancy² and therefore it is not advised for a late stage.

Pyometra management

Alizin® (10 mg/kg, SC) can be used in breeding animals that have no systemic complications. Absence of ovarian pathologies (e.g. ovarian cysts) is important before beginning of treatment. Two initial injections are given 24 hours apart, followed by

weekly injections until complete recovery. A modified protocol (injections at day 0, 2, 5, and 8) had high efficacy and there was no recurrence within 24 months.⁴ Vaginal discharge is observed within a few hours after the first injection. It is recommended that treated animals do not ingest the vulvar discharge and an Elizabethan collar is recommended. Additionally, it is important to combine the treatment with other therapies such as antibiotics, fluid therapy, and correction of gastrointestinal signs. The success rate is over 80%. Although, the combination of aglepristone with cloprostenol is described, it is not used frequently in our clinic. Subsequent fertility appears to be not affected by alizin® treatment.

Parturition induction

Inducing parturition and more frequently, scheduling a c-section, are indications for alizin®. Since induction of parturition is not a current request of clientele, limited data are available in clinical setting. In the studies performed to evaluate the efficacy of aglepristone to induce parturition, the results were similar to normal parturition. Timing of induction used for beagle bitches was 60 days after estimated LH surge⁵ and in other breeds it was 59 - 61 days postovulation.⁶ Oxytocin was also used in the above studies. Induction in bitches over 20 kg was less effective.

For the elective planned c-section cases, the protocol is to follow the bitch after 60 days from a well-estimated ovulation date to decide the time of alizin® injection (15 mg/kg SC). Serum progesterone concentrations are evaluated to ensure that the bitch has not started parturition (i.e. it is not at term) and the injection is given no more than 18 hours before the surgery to avoid onset of parturition. Ultrasonography is necessary to evaluate fetal viability and maturation.⁷ In our experience, verifying milk secretion before the procedure was necessary to decrease the risk of agalactia/hypogalactia in the first 24 hours after C-section. Our collective data from the last 10 years had a neonatal mortality (in the first 2 weeks of life) after planned C-section was 9.89%. Dead puppies were not further examined, but no obvious signs of prematurity were observed at the time of C-section.⁸ This is a safe procedure to avoid dystocia.

For feline mammary hyperplasia

Although this tumor can regress spontaneously, the hormonal component of the disease (exposure to progesterone) supports alizin® as a treatment option. The protocol is injections (15 mg/kg, SC) on days 1 and 2, then once per week until complete regression of mammary lesions. The success rate is over 90%, but in some cases, more than 5 injections are necessary to reach full recovery. If clinical signs are related to exogenous long-acting progesterone use, treatment should be repeated weekly for at least 5 weeks, even if regression of lesions occurred.⁹

Final considerations

Since the product is oil-alcohol based, the injection needs to be subcutaneous. After injection, a slight massage of the injection

site is necessary. If the volume of the injected solution exceeds 5 ml, the drug must be injected at multiple sites. Local pain at the site of injection (sometimes edema, skin thickening, ulceration, and localized lymph node enlargement) can be observed. In case of show dogs and dark color-coated animals, we prefer less exposed areas as injection sites. In our experience, systemic adverse effects as anorexia, excitation, depression, vomiting and diarrhea are infrequently observed. Alizin® is a welcome addition in the therapy and management of small animal reproductive problems.

Conflict of interest

None to report.

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