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PRACTICAL USE OF AGLEPRISTONE IN SMALL ANIMALS

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INTRODUCTION
Progesterone-receptor antagonists or antiprogestins are synthetic steroids that bind to the progesterone receptor, but fail to initiate activities normally initiated by progesterone. Therefore, by occupying the receptors they prevent the actions of endogenous progesterone. Progesterone is physiologically required for the maintenance of pregnancy, as it provides the hormonal stimulus for endometrial development and placental attachment. Furthermore, progesterone acts to maintain uterine quiescence by reducing the contractility of uterine musculature; its disappearance from the general circulation is required to allow the onset of parturition. Progesterone is however involved also in a few pathological conditions in small animals such as uterine and mammary diseases in the bitch and queen. Therefore, anti-progestins may have clinical applications in all of the above conditions, with the disruption of reproduction and termination of pregnancy being certainly the most relevant but not the only ones. All anti-progestins to date also have anti-gluocorticoid activity, but are more potent as antiprogestins than as anti-corticoids.

The affinity of aglepristone for progesterone receptors in vitro is three times greater than that of progesterone itself in the canine species, and it is thought to be nine times in the feline species. Aglepristone is a synthetic form of progesterone receptor antagonist which it can be used to block the action of progesterone at the uterine level both during pregnancy (causing foetal resorption, abortion, induction of parturition) as well as during stages other than pregnancy (to treat pyometra).

Aglepristone is commercially available in Europe for veterinary use as a non-aqueous injectable solution of 30 mg/ml for subcutaneous administration. The dosage for the bitch is 10 mg/kg repeated on two consecutive days, 24 hours apart. When used with this protocol, the maximal concentration of aglepristone in blood (280 ng/ml) is reached 2.7 days after administration, with a mean residence time of 6 days. Excretion of the molecule is performed essentially via the feces (90%). The dosage for the queen is reported to be 15 mg/kg, although not as much is known about efficacy of aglepristone in the queen as compared to the bitch.

Induction of abortion - In the mated bitch treated with Aglepristone, uterus is insufficiently stimulated, making implantation impossible or causing the embryo to be either resorbed or expelled, depending on the timing of Aglepristone treatment. The bitch should be carefully weighed prior to treatment, sides of injection site should be changed each time and massaged following the injection. From a clinical point of view, pregnancy can be terminated at an "early" (before implantation, therefore prior to pregnancy diagnosis, or day 22-24), "mid" (from implantation, which generally coincides with pregnancy diagnosis, around day 25, up to day 30-35) or "late" stage (after calcification of the fetal skeleton, from day 35). Early abortion is characterized by absence of clinical signs as embryos are typically resorbed, and an efficacy rate close to 100%. When mid or late abortion is performed, clinical signs such as foetal expulsion, mammary gland development and maternal behaviour patterns may be observed. This may cause inconvenience to the animal's owner, as well as raise ethical concerns. If dead foetuses are observed within the uterus following aglepristone injection, further treatment with aglepristone and/or prostaglandins aimed at emptying the uterus is warranted. Very prolific bitches with a large number of foetuses are thought to be more likely to experience partial abortion or complete abortion failure. Antibiotics are not required when carrying out a clinical abortion, unless there is a need to treat a known uterine infection.

When things go wrong – Treatment with aglepristone can be performed from the day of mismating. However, when a bitch is mismated it is always recommended to investigate the case history in order to confirm whether she has actually ovulated and diestrus has started. Performing a vaginal smear and collecting a blood sample to assay progesterone is warranted at this stage in order to avoid potential treatment failures. The actual length of action of aglepristone following two injections at 24 hr interval is approximately 10-12 days. Therefore, if a bitch gets treated with aglepristone after running away and/or being mismated early in her season, and this actually happens several days before ovulation, the concentration of the active principle may have already decreased to a minimum level by the time luteal progesterone starts to be secreted. If the bitch is subsequently mismated again during the same cycle, pregnancy may be established as luteal progesterone is able to bind to its receptors normally. It is therefore preferable to perform treatment at the end of oestrus, or at the beginning of dioestrus.

In mid- to late pregnancy, efficacy of aglepristone is approximately 95%, which means that occasionally a bitch may still be pregnant following treatment. Partial or complete failure of abortion may occur in very prolific bitches with a large number of foetuses. Because of such a risk, a thorough uterine ultrasound is...
warranted 8-10 days following the second injection to make sure that abortion is complete. Should a further treatment be necessary, aglepristone can be administered again once together with a course of prostaglandin to help uterine evacuation. When possible, early abortion should be preferred to mid abortion. Late abortion should be regarded as a last option, and treatment should be avoided in bitches more than 40 days into their pregnancy: as the interval between treatment and onset of abortion may be as long as 8-10 days, if a bitch gets treated on day 45 she may well whelp live puppies 10 days later. The use of aglepristone may sometimes shorten the interoestrus interval following treatment to 5 months but does not affect future fertility of the bitch.

Induction of parturition - The competitive binding of aglepristone on progesterone receptors mimics the final drop of serum progesterone concentration observed prior to natural parturition. The drop in progesterone causes cervical opening while the myometrium becomes sensitive to the action of oxytocin. Subsequent administration of oxytocin then provokes uterine contractions and induction of labour. Aglepristone also is thought to bring about respiratory maturity in puppies (alveolar deposition of surfactant), although no data is available to substantiate this claim. At any rate, parturition can be successfully induced on day 58 of gestation by giving two injections of aglepristone 9 hrs apart. Treatment can be followed by repeated injections of oxytocin until the last pup is expelled. Although initial experimental data seem to confirm the safety of such use of aglepristone, inducing parturition in a bitch is always a very delicate and challenging event for a veterinarian as anything that goes wrong is inevitably considered as due to the procedure. It is often difficult to know the exact date of ovulation, which makes it difficult to date gestation accurately; also, our knowledge of the state of prematurity of puppies before day 58 is still incomplete at the present time. Reasons which may justify a decision to induce parturition in the bitch are very rare including abnormally long gestation, toxoaemia or pre-partum eclampsia. A risk of dystocia (such as relative or absolute disproportion between foetus and mother), or of uterine inertia cannot constitute reasons for inducing parturition. Likewise, a desire to plan parturition (as is the case for other species) to ensure that it occurs under the best possible circumstances (at a time when it is easy to be monitored because of presence of staff in the clinic or availability of the breeder) should be regarded as unacceptable and unethical as a reason for inducing parturition. The injection of 15 mg/kg of aglepristone 24 hours before a Caesarean section is thought to produce the final maturation of puppies as well as to improve uterine conditions for surgery and to speed up uterine involution and placental detachment following surgery (although no data are currently available to justify such a use).

Treatment of pyometra - Because of its marked affinity for progesterone receptors in the uterus, aglepristone can be used for the medical treatment of pyometra in bitches and queen thus preventing the damaging effects of progesterone. While ovariohysterectomy remains the basic treatment for pyometra in bitches, the conservative medical treatment for pyometra is indicated for bitches intended for breeding or in bitches who are old or in critical conditions and therefore at surgical risk or whenever the owner refuses to consider surgery. Medical treatment sometimes allows delaying ovariohysterectomy, at a time when the bitch is in better condition, after uterus emptying. Because of the absence of progesterone from the general circulation following parturition, post-partum uterine infections are not an indication for Aglepristone treatment. Whenever considering using aglepristone in a female with pyometra, the patient general conditions should be carefully assessed to rule out peritonitis or a septic syndrome, renal failure, reactive hepatitis or disseminated intravascular coagulation. As with any case of pyometra, a careful clinical and ultrasound examination, additional blood cell count and biochemistry assays should always be carried out. Medical treatment should be accompanied by careful monitoring, fluid administration if necessary, frequent reassessment of the animal condition and the owner should be informed of the risk of treatment failure. In most cases, it is preferable to hospitalise the bitch.

Administration of the usual dosage of 10 mg/kg on days 1, 2, 8 and then also 15 and 28 depending on the clinical situation has resulted in positive results in bitches with both open cervix and closed-cervix pyometra. The use of aglepristone can be associated with PGE provided that cervical opening has occurred. In bitches with closed cervix pyometra, administration of aglepristone is often followed by cervical opening within 24-48 hrs. The combination with prostaglandins is recommended from the 3rd day of treatment onwards, once the cervix has opened. Because of their uterotonic effect, prostaglandins provide faster emptying of the uterus while their specific luteolytic activity strengthen the effect of aglepristone. When using a combination treatment, prostaglandins are generally administered daily except on the days when aglepristone is given. Reported associations of aglepristone + prostaglandins include either PGF2α compounds such as Cloprostenol (1 µg/kg/24hrs) or Dinoprost (25 µg/kg BID on day 3, 50 µg/kg BID on day 4, followed by 70 µg/kg BID from day 5 on) or PGE compounds such as misoprostol (10 µg/kg orally BID). For most cases, 3 subcutaneous injections of aglepristone at a dose of 10 mg/kg on D1, D2 and D8 may be sufficient (injection at D15 optional) if aglepristone is used together with prostaglandins (aglepristone on day 1, 2 and 8, prostaglandins on day 3-7). Repeating aglepristone on day 15 and 28 can be done depending on patient’s conditions. However, one should never expect any such treatment to be curative as each bitch or queen behaves differently. Therefore, the treatment with prostaglandins should be continued until when uterine conditions have return to normality based on ultrasound and absence of vulvar discharge. Specific antibiotic therapy is strongly recommended jointly with aglepristone and prostaglandins; antibiotics should also be continued as long as uterine conditions remain abnormal and/or a purulent vulvar discharge is present.
Antiprogestins in cats.

Aglépristone can induce abortion in cats. The suggested dosage is higher than in the dog, being 15 mg/kg twice 24 hrs apart. There is no information on the effect of aglépristone on pyometra in the queen, but efficacy for this indication is thought to be the same as in dogs. Aglépristone has also been reported to be effective in treating feline mammary hypertrophy in queens using a dosage of 10 mg/kg for 2 consecutive days, to be repeated weekly for 1-4 weeks.

**Suggested Readings**

6. Galac(S.), Kooistra(H.S.), Butinar(J.), Bevers(M.M.), Dieleman(S.J.) Voorhout(G.) and Okkens(A.C.): Termination of mid-gestation in bitches with aglépristone, a progesterone receptor antagonist – Theriogenology, 2000, 53: 941-950.