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Clinical Use of Anti-Progestins in the Bitch (23-Feb-2001)

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Introduction

In the bitch, progesterone plays a critical role in the establishment and maintenance of pregnancy. At the onset of estrus, serum progesterone rises. Progesterone permits the maturation of uterine cells so as to prepare them for implantation. After fecundation, progesterone controls uterine secretions which nourish the embryo until implantation between days 18 and 23. Lastly, progesterone inhibits uterine contractions throughout the 65th or so days of pregnancy.

This physiological regulation of pregnancy by progesterone is the reason that anti-progestins can be used for pregnancy termination and the induction of parturition in dogs. At least one anti-progestin is available for clinical use in dogs in selected European countries.

Antihormones and Antiprogestins

Antihormones have the ability to bind particular hormonal receptors without eliciting a hormonal message or action (Fig. 1). Often, antihormones increase the synthesis and plasma concentrations of other hormones by the inhibition of the normal feedback control of those hormones.

Antiprogestins are synthetic steroids which bind with great affinity to progesterone receptors without any of the effects of progesterone. In bitches, two antiprogestins have been studied: mifepristone (RU 486) and aglepristone (RU 534) (Fig. 2).



Figure 1. Binding competition between progesterone and aglepristone for the progesterone receptors and consequences. - To view this image in full size go to the IVIS website at www.ivis.org . -

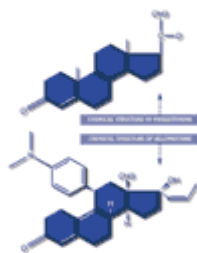


Figure 2. Chemical structures of aglepristone and progesterone. - To view this image in full size go to the IVIS website at www.ivis.org . -

Mifepristone is a progesterone and glucocorticoid antagonist. It is more potent as an anti-progestin than as an anti-corticoid. In the absence of progesterone or cortisol, mifepristone can have a moderate agonistic effect [1]. Mifepristone was developed by Roussel Uclaf laboratories for application in humans. In pregnant women, mifepristone (RU486) is able to interrupt early pregnancy in 80% of cases without any major side effects [2]. To improve its efficacy, mifepristone is currently used in combination with low doses of prostaglandin analogs such as misoprostol. The efficacy of combined treatment (mifepristone plus misoprostol) is 96% [3]. Mifepristone has been demonstrated to induce direct luteolysis [4] and has an anticorticoid activity [5]. This drug is not available for veterinary use.

Aglepristone is an antiprogestin recently developed by Roussel Uclaf veterinary research specifically for animal use. It is available in France, Norway and Sweden under the name of Alizine ® distributed by Virbac laboratories (Carros, France)

(Fig. 3). Aglepristone competes with progesterone for uterine receptors with a fixating rate of 3 (versus 1 for progesterone) in the bitch [6]. In the queen, the fixating rate is 9.



Figure 3. Alizine® - commercial presentation. - To view this image in full size go to the IVIS website at www.ivis.org . -

Pregnancy Termination

Mifepristone

In pregnant bitches, mifepristone was effective if administered after day 30 of gestation [7-14]. The protocol used was the oral administration of 2.5 mg/kg, twice a day for 4 to 5 days. Pregnancy was terminated without side effects within 3 to 4 days after treatment.

Aglepristone

This drug can be used for pregnancy termination from mating date until 45 days after mating (Fig. 4).



Figure 4. Protocol of Alizine ® administered twice, 24 h apart, for pregnancy termination in dogs. Mating on the day after ovulation in mid-estrus will normally result in a pregnancy with parturition occurring 62 days later. Alizine can be used any time up to day 45 for safe effective termination of pregnancy, including early pregnancy between Day 0 and 21 after mating. In mid pregnancy it can be used in bitches in which an unwanted pregnancy has been confirmed by ultrasound between Day 22 and 30. In contrast, proposed uses of estrogens are only effective between Days 0 - 3. The use of prostaglandin for pregnancy termination is often limited to Days 30 - 45 following pregnancy diagnosis, because of the need for multiple, frequent administrations and side-effects. - *To view click on figure -*

Protocol - Bitches are injected subcutaneously with 0.33 ml/kg/day repeated once 24 hours later. The preparation is an oily-alcohol solution containing 30 mg of aglepristone per ml. (Alizine ®)

Efficacy - in a control study (104 bitches), the early administration of aglepristone after mating (Day 0 - Day 25) always resulted in abortion (confidence interval from 90% to 100% (P<0,05)). Its later administration (Day 26 - Day 45) induced abortion in less than seven days in 95.7 % of cases studied (confidence interval from 89% to 100% (P<0,05)) [8] (Table 1).

Table 1. Rate of Pregnancy Termination after Aglepristone Administration.		
Study	Early pregnancy termination Day 0 to day 25	Mid pregnancy termination Day 26 to day 45
At Vet School	100 % (35/35)	95.7 % (66/69)
At Practitioner's	100 % (139/139)	94.4 % (117/124)

Similar results were obtained in a field-trial study on mid-pregnancy termination (124 bitches). Fourteen days after the first injection of aglepristone, 94.4% of the bitches had no foetal image during an ultrasonography examination of the uterus (confidence interval from 89% to 98% (P<0,05)). Embryonic resorption occurred for bitches treated in early pregnancy. In mid pregnancy fetal expulsion occurred 4 days after the first aglepristone injection for 50% of the bitches and within 7 days for all the bitches. It is clinically important *to confirm the efficacy* of the treatment. *An ultrasonographic exam of the uterus must be performed 8 days after treatment in mid-pregnancy or 20 days after treatment in early pregnancy.*

Safety - Administration of aglepristone can induce a localised inflammatory reaction which disappears within two weeks. This may be due to the oily-alcohol solution of Alizine ®. *To prevent this reaction, practitioners are advised to massage the skin at the injection site.* Early pregnancy termination, (before 25 days post mating), does not induce either clinical observation or modification of the ultrasonographic image of the uterus.

Termination in mid-pregnancy induces foetal expulsion. Brown mucoid vaginal discharges are observed 24 hours before

foetal expulsion and continued for 3 to 5 days. During the abortion itself, some clinical signs such as slight depression, transitory anorexia, mammary gland congestion can be present. Such signs are also often observed at physiological parturition time and in late pregnancy termination with prostaglandins or antiprolactin-drugs [9].

There are no repercussions on reproductive function apart from the fact that, in some bitches, there is a decrease in the interoestrous interval from one to three months [8]. *Consequently bitches may be observed returning to estrus as early as 45 days after pregnancy termination.*

Hormonal Variation - Aglepristone does not modify plasma concentrations of progesterone, prostaglandins, oxytocin or cortisol within 24 hours after its administration but induces an increase in concentrations of prolactin within 12 hours in bitches treated in mid pregnancy (Fig. 5). This can explain the mammary gland congestion typically observed after mid-pregnancy termination. Shortening of the interoestrous interval and prolactin release seems to prove a direct or indirect action of aglepristone on hypothalamic-pituitary axis. As an abortifacient, aglepristone acts like a progesterone antagonist, at the uterus level and does not have direct and immediate luteolysis properties. Termination of pregnancy occurs in the presence of high plasma progesterone concentrations (Fig. 6). Foetal expulsions in late pregnancy termination are accompanied by an increased prostaglandin F metabolites (PGFM) concentrations and decreased progesterone concentrations, however, oxytocin and cortisol remain at a basal level.

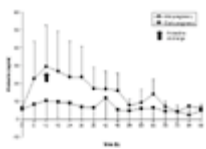


Figure 5. Plasma prolactin concentrations, demonstrating specific prolactin discharge observed at 12 hours of aglepristone administration for mid-pregnancy termination. - To view this image in full size go to the IVIS website at www.ivis.org . -

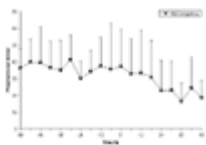


Figure 6. Mean (\pm SD) peripheral plasma concentrations of progesterone for bitches treated in mid-pregnancy. Time E was the mean foetal expulsion time. - To view this image in full size go to the IVIS website at www.ivis.org . -

Parturition Induction

Considering the major role progesterone plays in maintaining pregnancy, it follows that antiprogesterin can be used to induce parturition. In pregnant women, it has been demonstrated that mifepristone (RU 486) induces uterine contractions and cervix maturation [13]. Used at term, administration of mifepristone induces an effective labor, within 72 hours, in 58% of treated women versus 22% in the control group [11]. In bitches, after 56 days of pregnancy, mifepristone induced parturition between 26 and 70 hours [6,15,16]. Some bitches could not expel the fetuses and a caesarean was performed. For others, expulsion time was between 18 and 45 hours. In addition, the experimental termination of pregnancy after 55 days with aglepristone resulted in the expulsion of live pups [8].

Protocol - To induce parturition, bitches are injected subcutaneously with 0.05 ml/kg (15 mg/kg) of aglepristone (Alizine®), after 58 days of pregnancy, then 24 hours later and every 2 hours afterwards, with 0.15UI/kg of oxytocin until the end of parturition.

Efficacy - Results to date suggest that the mean time of parturition onset is 31.6 ± 3.6 hours after aglepristone administration and mean expulsion duration is 4.5 ± 1.8 hours. As a result, if aglepristone is administered at 8 AM, treated bitches will begin parturition the next day between 2 and 6 PM and will finish between 7 PM and 11 PM.

Safety - At birth, 93.10% of the pups were alive. Forty-eight hours later, the survival rate was 86.21%. Mortality rates were comparable to those observed under natural conditions [17]. This confirms the safety of aglepristone [9,10] and the possibility of the practical use of such a protocol.

Hormonal Variation - Progesterone peripheral plasma concentrations increase after injection of aglepristone and bitches finish parturition with a progesterone concentration higher than 8 nmol/L. This increase can be due to the binding of progesterone receptors by aglepristone in place of natural hormone. The increase in plasma progesterone concentrations may also be due to an hypothalamic effect of aglepristone on GnRH neurons that results in increased pituitary secretions (FSH and LH) which might stimulate corpora lutea cells. A similar initial increase in progesterone concentrations was observed in the induction of parturition in sheep using mifepristone [12].

Administering aglepristone does not induce a direct or indirect luteolysis effect and does not modify plasma concentrations of oxytocin or cortisol during the first 24 hours. Four hours after aglepristone administration, PGFM concentrations significantly increase, but after the initial increase, PGFM concentrations remain at a low levels. The authors confirm that antiprogesterin administered at the end of pregnancy does not induce a peak of prostaglandin-F2 alpha as has physiologically been observed at parturition time.

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