Clinical application of a competitive progesterone receptor blocker (aglepristone) in small animal reproduction

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Introduction

Although available in certain European countries for a number of years, aglepristone has only been registered and therefore readily available in South Africa since August 2009. Currently, the drug is registered for pregnancy termination in dogs only. However, an abundance of literature exists supporting its use for other purposes in cats and dogs. This short communication outlines the use of aglepristone in clinical settings other than pregnancy termination. The practitioner is reminded that such use has to be accompanied with informed consent from the owner.

Mechanism of action

When a hormone binds to its receptor, conformational change of the receptor-hormone complex takes place and this is often the trigger for initiation of transcriptional activity. Drugs that are classified as receptor blockers compete with their agonists for the binding sites to receptors but do not exert complete signal transduction. Depending therefore on the degree in change of receptor conformation, as well as subtypes of receptors and receptor mutations, competitive receptor blockers may have inherent agonistic activity [15]. Aglepristone competitively inhibits the binding of endogenous progesterone to the nuclear progesterone receptor without initiating transcription [14]. The inherent agonistic activity that is displayed by aglepristone, along with the similar role of progesterone in the non-pregnant and pregnant bitch and queen, accounts for its use in different clinical settings. When comparing the combination therapy of cloprostenol and cabergoline to cloprostenol and aglepristone, Martin [19] showed that although both treatment combinations have the same abortive action, their sequence of events on the CL is different. Corpora lutea (and their associated blood vessels) from aglepristone/cloprostenol treated animals showed less outspoken degeneration. In an attempt to further elucidate the luteal events associated with aglepristone-induced abortion, Kowalewski [17] suggested that luteolysis associated with aglepristone points to a role of luteal progesterone as an autocrine factor in a positive loop feedback system controlling availability of progesterone, steroidogenic acute regulatory protein (StAR) and 3α-hydroxysteroid-dehydrogenase (3-HSD). Interestingly, bitches treated with aglepristone display a drop in rectal temperature, similar to the prepartum bitch [3]. Considering that this happens in the face of elevated plasma progesterone levels provides evidence for hypothalamic effects of aglepristone.
Induction of parturition

It is important when reading literature concerning pregnancy and parturition in the bitch, that a clear understanding of reproductive physiology exists. A bitch can be said to be 57 days pregnant, if measured from the day of onset of cytological dioestrus. Since the LH-surge in a bitch occurs 8 ± 1 days before the onset of dioestrus, it follows that a bitch can also be seen to be pregnant for 65 ± 1 days if measured from the LH-surge [16]. In the context of the availability of assays for testing of LH in South Africa, it should be borne in mind that the LH-surge is often determined indirectly by referring to the very good correlation between the LH-surge and the rise of plasma progesterone concentration (PPC) to a level above 6nmol/l. Ovulation in the bitch occurs 2 ± 1 days after LH-surge, and therefore gestational length is often cited as 63d, if measured from the day of ovulation. The latter gestational length more accurately follows convention – most species’ gestational length is measured from the day of ovulation.

Baan [2] demonstrated normal parturition and pup survival in 6 bitches induced with aglepristone. The protocol for induction was two injections of aglepristone at 15 mg/kg, 9h apart on day 58 of pregnancy. Expulsion of the first pup was observed between 32 and 56 hours after the first treatment. The same research group investigated the hormonal changes associated with aglepristone-induced parturition [1]. It was shown that aglepristone-induced parturition is associated with incomplete luteolysis, an altered PGFM profile and elevated postpartum cortisol concentrations when compared to spontaneous whelping bitches. The latter finding could point towards the involvement of the adrenal gland in aglepristone-induced parturition. Fieni [5] combined oxytocin injections with aglepristone to induce parturition. Twenty two pregnant Beagle bitches were injected with 15 mg/kg aglepristone on day 58 of pregnancy, a second injection of aglepristone 24 h later and then followed by hourly injections of 0.15 IU/kg oxytocin until expulsion of the last pup. Parturition in the treatment group was normal in all respects, as was pup survival rate at 48h, 7 days and at 7 weeks of age. These results were also confirmed for bitches of different age and size to the original treatment group of adult Beagles [7]. In this study, a litter of Yorkshire Terrier pups were born prematurely and did not survive beyond 29h post-delivery. The reason for the delivery of premature pups was not investigated and the significance of this finding remains unknown.

Aglepristone has also been used as an agent to facilitate the performance of elective Caesarian section [18]. In this study, aglepristone was administered to 37 pregnant bitches at 15 mg/kg on day 59 or 60 of pregnancy, and Caesarian section was performed between 20 and 24 h after administration. In all cases, progesterone remained elevated above 6nmol/l at the time of surgery. No post-operative clinical complications were reported in any bitches or their pups. No pups showed any sign of prematurity and 2.6% died in the first 2 week after delivery. This figure compares favourably with neonatal death rates in bitches whelping naturally.

The triggering mechanism for parturition in the bitch remains unclear, and this has contributed to paucity of clinically useful information to reliably induce parturition in the
While numerous studies have reported the successful use of aglepristone, either alone or in combination with oxytocin, to induce parturition in the bitch, these studies have thus far not produce statistically powerful results. This can mostly be attributed to low numbers of animals in the experiments. Nevertheless, experimental results have been corroborated by various reports, and therefore the extra label use of aglepristone for induction of parturition can be justified.

**Treatment of uterine infections**

A recent survey among Norwegian practitioners [21] reported that the most common treatment for pyometra was ovariohysterectomy, combined with fluid administration and antimicrobial therapy. It is probable that a similar survey in South Africa will yield similar results. From a medical point of view, this approach is the safest, but it eliminates future breeding potential.

There is currently no registered medical treatment available in South Africa for pyometra in dogs and cats. The practitioner wishing to treat a case of pyometra medically, therefore has to not only inform the client of the extra label use of a drug for this purpose, but also make a rational choice of treatment. To be able to do this, peer-reviewed literature should be consulted. The bulk of literature supporting medical treatment of pyometra focuses on the use of natural prostaglandin F2α twice daily at doses ranging from 25 to 250 mcg/kg. A smaller set of articles support the use of prostaglandin analogues and prolactin inhibitors (dopamine agonists). A growing body of evidence also supports the use of progesterone receptor blockers, either alone or in combination with prostaglandins. As opposed to all the other drugs suitable for use in cases of canine pyometra, the use of aglepristone is associated with very few side effects.

The most common protocol for the use of aglepristone in treatment of canine pyometra is three subcutaneous injections at 10mg/kg on day 1,2 and 7 [13,22]. Follow-up evaluation and treatment if necessary, is done on day 14. The first study of the use of aglepristone for treatment of canine pyometra [13] reported its use in 31 bitches. Treatment resolved clinical signs and cleared the uterus of purulent fluid in 22/31 (71%) of the cases. Interestingly, treatment failure was associated with a presenting progesterone level of less than 3.2 nmol/l or abnormal ovarian function (ovarian cysts). In a study involving 52 bitches [22], 48 bitches (92.8%) recovered from clinical signs and had empty uteri after treatment with aglepristone alone, following the treatment protocol outlined above. In three bitches treatment did not lead to evacuation of the contents of the uteri and ovariohysterectomy had to be performed. These three bitches all had ovarian pathology observed *intra operationem*. One bitch died of renal insufficiency. Unfortunately, breeding data of animals from this study, is only available for 6 animals, making it a very small data set, but 5/6 (83.3%) had normally sized litters following treatment. The study also reported that interoestrus interval was only shortened in 7/37 bitches (18.9%).

Wehrend [24] reports the successful use of aglepristone in nine bitches diagnosed with closed cervix pyometra. The bitches were treated with 10mg/kg of aglepristone subcutaneously on days 1, 2 and 7, while broad-spectrum antimicrobial therapy was
maintained. In all bitches, the cervix opened and a putrid discharge could be observed from the vulva within 72h after the first aglepristone administration. It should be noted that the average age in the study was 8.2±2.6 years, suggesting that aglepristone is also safe in older bitches.

Several studies report the use of aglepristone in combination with cloprostenol [4,10]. Gobello studied the efficacy and safety of two protocols combining aglepristone and cloprostenol for the treatment of open cervix pyometra in bitches [10] and confirmed that the addition of repeated cloprostenol treatments (group II; 7 bitches) resulted in significantly lower plasma progesterone concentrations. All bitches were treated with 10mg/kg aglepristone on days 1, 3 and 8. Bitches in Group I received 1mcg/kg cloprostenol on Days 3 and 8, while bitches in Group II received the same dose of cloprostenol every other day from day 3 until day 12 or 15 if not cured. Redevelopment of pyometra in this study was reported to be 20%, and the only bitch for which subsequent breeding data was available, whelped a normal litter. Fieni reported a 90-day success rate for treatment of pyometra with a combination of aglepristone and cloprostenol of 27/32 (84.4%) [4]. This compares with 12/20 (60.0%) when aglepristone is used on its own. Their protocol consisted of 10mg/kg aglepristone on days 1, 2 and 8 and 1mcg/kg cloprostenol on days 3-7. The addition of cloprostenol in this study therefore significantly improved the 90 day success rate. No statistically significant difference was observed in the recurrence rate between the two protocols.

The use of aglepristone in cats

In a review of the therapeutic options available for suppression of oestrus and termination of pregnancy in the cat, Goericke-Pesch [11] expresses the opinion that only aglepristone is justifiable regarding tolerance and animal welfare. The successful use of aglepristone for mid-gestation pregnancy termination in the cat has been reported by Fieni [6] and Georgiev [8]. Treatment at 10 mg/kg aglepristone on two consecutive days with 24 hour interval resulted in expulsion of fetuses in 88.5% (61 queens in study) and 87% (23 queens in study) of queens treated. Side effects were limited to brief periods of depression and anorexia surrounding foetal expulsion. A further study by Georgiev shed some light on the mechanism through which aglepristone caused abortion in queens [9]. On histological sections of a mid-gestation pregnancy termination it was noted that gaps appear within the paraplacenta and the placental girdle. The gaps were filled with blood originating from damaged venules, whilst arterioles remained. The end result of bleeding from damaged venules is bleeding into the uterine lumen and consequent utero-placental detachment.

Nak [20] reported successful treatment of 9/10 (90%) queens for pyometra with aglepristone at 10 mg/kg on days 1,2 and 7. The treatment was associated with very few side effects and no recurrence was observed for a period of two years.

Aglepristone has also been used with success in the treatment of feline mammary fibroadenomatous hyperplasia, using aglepristone at a dose rate of 10 mg/kg on 4-5 consecutive days [23] or at 20 mg/kg per week for a period of 1-4 weeks [12].
References


