ABSTRACTS

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COMPARISON OF TWO DOSES OF THE GNRH ANTAGONIST, ACYLINE, FOR PREGNANCY TERMINATION IN BITCHES

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Introduction - GnRH antagonists competitively block GnRH receptors sites at the pituitary gland. They have an immediate action which make them particularly useful when a rapid inhibitory effect on the gonadal axis is required [2,6]. Until depot formulations of antagonist were available, the management of point endocrine situations seems to be the main indication for antagonists [1]. In female dogs, a practical reproductive situation that usually requires a rapid intervention is unwanted pregnancy termination. Safe, efficient, single dose abortive drugs have not been developed in this species yet. Acyline is a new, third generation GnRH antagonist that has been found in human beings to be more effective at suppression and maintenance of suppression of gonadotrophins than previous antagonists in a dose dependent manner [3,4].

Objectives - It was, therefore, the aim of this study to test the efficacy and clinical safety of a low and high dose [3,4] of the GnRH antagonist, acyline, on pregnancy termination in female dogs. Additionally, the effect of acyline on progesterone (P₄) serum concentration was described.

Materials and methods - Twenty-one cross and pure-bred, pregnant (25 to 35 days from first mating) bitches were randomly assigned to one of the following pharmacological protocols: acyline (NIH, MD, USA) 110μg/kg SC (ACY-L, n = 6); acyline (NIH, MD, USA) 330μg/kg SC (ACY-H, n = 8) or placebo (PLACE, n = 7).
All the bitches were followed up daily during 15 days after treatments. Followed up included evaluation of behavior, vulvar discharge, abortion and eventual appearance of side effects. Blood samples for P₄ serum determinations were collected before and on days 2, 5, 7 and 14 after treatment. When clinical suspicion of pregnancy termination first appeared the bitches were ultrasonographically monitored to look for resorption or abortion signs. If no clinical signs of interruption appeared, ultrasound examination was carried out on days 7 and 14.
The frequency of bitches achieving pregnancy termination and/or side effects in each group was analyzed by PROC FREQ (SAS®, [5]). Progesterone serum concentrations and days to pregnancy termination were compared by least squares analysis of variance using the General Linear Model Procedure (PROC GLM; SAS®, [5]). The mathematical model included the main effects of group and day (-1, 2, 5, 7, 14) and their interaction.

Results - All ACY (14/14) but none PLACE (0/7) groups bitches terminated their pregnancy (P < 0.01). ACY-L and ACY-H groups interrupted their pregnancy 7 ± 1.9 and 6.4 ± 1.3 (n =8; P > 0.1) days after treatment, respectively with a range of 2 - 12 for both treatments. In all the cases, termination occurred by abortion which was confirmed by ultrasound examination. A significant interaction between treatment and day was found (P < 0.01) for P₄ serum concentrations when PLACE was compared to both ACY groups. Although, no difference was found for this hormone between ACY-H and ACY-L groups (P > 0.1). In both ACY groups P₄ concentrations diminished throughout the study. The decreasing rate varied among individual animals and was closely related to the time of abortion. Pregnancy termination was preceded or accompanied by a fall of P₄ (< 2ng/mL) in all the cases. After termination, P₄ remained basal until the end of the study. Conversely, in PLACE animals gestation progressed normally and P₄ serum concentrations were maintained non basal. None of the bitches presented undesirable effects related to the treatments.
In line with a previous abstract [8], in the present study, the third generation GnRH antagonist acyline suppressed luteal function and terminated pregnancy in all the treated bitches. Although, dose dependent effects were previously described for these compounds [3] no significant differences were found for the rapidity of the aborting effect between the high and the low dose. Considering that luteolysis was probably due to the antagonist induced LH deprivation, these results confirm that LH is needed to maintain corpus luteum of canine pregnancy. Furthermore, \( P_4 \) remained basal after abortion, demonstrating that GnRH antagonists caused permanent luteolysis in mid luteal phase. In contrast to earlier studies using the second generation antagonists [9] in the present trial clinical safety seemed to be warranted.

It is concluded that the third generation acyline safely terminated mid pregnancy irreversibly decreasing \( P_4 \) serum concentrations. The outcome of this study identifies the new GnRH antagonists as promising single dose, efficacious and safe drugs for abortion induction in this species.

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References