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Clinical evaluation of different applications of misoprostol and aglepristone for induction of abortion in bitches

A.R. Agaoglu [a,*], S. Aslan [d], B. Emre [b], Ö. Korkmaz [b], E.S. Özdemir Salci [c], M. Kocamuftuoglu [a], K. Seyrek-Intas [c], S. Schäfer-Somi [e]

[a] Department of Obstetrics and Gynecology, Faculty of Veterinary Medicine, University of Mehmet Akif Ersoy, Burdur, Turkey
[b] Department of Obstetrics and Gynecology, Faculty of Veterinary Medicine, University of Harran, Sanliurfa, Turkey
[c] Department of Obstetrics and Gynecology, Faculty of Veterinary Medicine, University of Uludag, Bursa, Turkey
[d] Department of Obstetrics and Gynecology, Faculty of Veterinary Medicine, University of Ankara, Ankara, Turkey
[e] Centre for Artificial Insemination and Embryo Transfer, University of Veterinary Medicine Vienna, Austria

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ABSTRACT

The aim of the present study was to compare the clinical and endocrinological effects of different applications of misoprostol (MIS) and aglepristone (AGL) for the induction of abortion in bitches. For this purpose, 28 healthy pregnant bitches from different breeds, ages, body weights (Body weigt, BWs, 10–40 kg), and between Days 25 to 35 of gestation were used. Bitches were randomly assigned to four groups. In group 1 (GI, n = 7), AGL (10 mg/kg BW, s.c. on 2 consecutive days); in group 2 (GII, n = 7), AGL (as in GI), intravaginal MIS (IVag, 200 μg for bitches with ≤20 kg BW, 400 μg for bitches with >20 kg BW, daily intravaginally until completion of abortion); in group 3 (GIII, n = 7), AGL (as in GI), ICVag (as in GII), per os MIS (400 μg for bitches with ≤20 kg BW, 800 μg for bitches with >20 kg BW, daily orally, until completion of abortion); in group 4 (GIV, n = 7), AGL (as in GI), per os MIS (as GIII) were used. Clinical, vaginal, and ultrasonographic examinations were performed daily until abortion was completed. For measurement of serum progesterone, blood samples were collected in all groups immediately after the first AGL administration and every other day until completion of abortion. No statistical differences were found between groups concerning the duration until completion of abortion after treatment (nonsignificant); however, in GII, one bitch completed abortion 2 days after the start of treatment.

1. Introduction

Unwanted pregnancy in breeding bitches is a serious problem for the owners. There are several reasons for this such as the difficulty of rearing and later adoption of the puppies. Many dog owners prefer pregnancy termination by medical application to avoid postoperative complications such as urinary incontinence, weight gain, and changes in behavior. For these reasons, intense research to improve pregnancy termination in bitches is ongoing, and abundance of studies has meanwhile been published [1–5]. These methods such as repeated applications of low doses of PGF2α during midpregnancy for a week [6,7], antiprolactin treatments in the second half of pregnancy [8,9], antiprogestin treatments during any time of pregnancy and combinations have been used successfully [1,2,10]. Antiprolactin and PGF2α treatments have some side effects such as vomiting, defecation, anorexia, and anxiety. The side effects of antiprogestin are negligible [11–13]. In bitches, antiprogestins like aglepristone (AGL) are therefore preferably used for induction of abortion [1,14].

* Corresponding author. Tel.: +90 2482132239; fax: +90 2482132001
E-mail address: rehaagaoglu@mehmetakif.edu.tr (A.R. Agaoglu).

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Aglepristone (RU 534) is a synthetic steroid that binds with higher affinity to progesterone (P4) receptors than the natural progesterone, thus inhibiting its biological effect [2,5,15]. The administration of AGL between Days 0 and 45 after mating prevented pregnancy or induced resorption or abortion within 7 days without side effects in bitches [2]. In another study, after two applications of AGL at a dose of 10 mg/kg body weight (BW) 24 hours apart, completion of abortion occurred within 10 days [1].

Misoprostol (MIS) is a synthetic prostaglandin E1 analog, and usually used for the prevention and treatment of gastrointestinal ulcers caused by prostaglandin inhibitors (Non steroidal anti-inflammatory drugs, NSAIDs) [16]. However, MIS increases the activity of collagenases in the cervix, and causes an increase in elastase, glycosaminoglycan, and hyaluronic acid in the cervix. In addition, MIS is a highly effective uterotonic [17]; MIS increases intracellular calcium levels, and causes contractions of the myometrial muscle [18]. For these reasons, MIS became one of the most useful compounds for termination of pregnancy in women [19]. Misoprostol is characterized by rapid absorption from mucosal membranes [20]. The administration can be via different routes such as vaginal, sublingual, buccal, and per os [21]. The transvaginal MIS administration for induction of abortion was firstly described by Leihair, et al. [22]. Some pharmacokinetic researchers showed that vaginal applications are three times more biologically efficient than per os applications [23]. Intravaginal MIS administration was investigated for induction of parturition, abortion, and cervix dilatation in heifers [24], ewes [25], mares [26], and bitches [27]. In one study, Agaoglu, et al. [1] concluded that the combination of MIS and AGL is more effective for cervical opening in bitches, than the sole application of AGL. In one study, the combination of intravaginal MIS with subcutaneous alphaprostol and oral cabergoline (CAB) used for induction of abortion, led to earlier opening of the cervix than application of alphaprostol and CAB without MIS [27].

Although there is no study in animals for induction of abortion with oral MIS, there have been many studies in humans. Oral intake of MIS is rapidly followed by absorption from the intestinal canal, and metabolized to its active metabolite in the liver [18]. One group compared oral versus vaginal MIS, and found no difference in the two routes of administration in women [28].

In the present study, we aimed to evaluate the effectiveness of different combinations of oral and vaginal MIS with AGL for termination of pregnancies in bitches.

2. Material and methods

2.1. Animals and experimental groups

In this study, a total of 28 healthy pregnant bitches of different breeds, ages, and BWs (10–40 kg), between Days 25 and 35 of gestation, were used. Bitches were randomly assigned to four groups: GI (n = 7): AGL (10 mg/kg BW, s.c. on 2 consecutive days); GII (n = 7): AGL (as in GI), intravaginal MIS (IVag-MIS, 200 μg, one tablet, for bitches with ≤20 kg BW; 400 μg, two tablets, for bitches with >20 kg BW; tablets were daily administered intravaginally close to the external orifice of the cervix uteri via tubular vaginoscope, until completion of abortion) [27]; GIII (n = 7): AGL (as in GI), IVag-MIS (as in GII), per os MIS (400 μg, two tablets, for bitches with ≤20 kg BW; 800 μg, four tablets, for bitches with >20 kg BW, daily orally, until completion of abortion); GIV (n = 7): AGL (as in GI), per os MIS (as in GIII). If AGL volume was greater than 5 mL, injection was given at more than one site in all groups.

Animal experimentation was approved by the respective local authority (Local Ethics Committee on Animal Experiments of Mehmet Akif Ersoy University, Burdur, Turkey; approval no: 2013-13).

2.2. Examinations and sampling

Diagnosis of pregnancy was confirmed by ultrasonographic examination (6.5 MHz probe; KAI XIN, KX5500). The stage of pregnancy was determined using reference equations by measuring fetal and extrafetal structures [29,30].

The genital ultrasonographic and general examinations were performed daily until abortion was completed. Side effects (vomiting, apathy, weakness, and so forth) and clinical genital examination findings such as onset of vaginal discharge, cervical dilatation, and color of vaginal discharge were monitored and recorded daily. Vaginal discharge was monitored in terms of color change from start to end of the treatment (white, red-brownish, green-brownish). Cervical dilatation was diagnosed by vaginoscopic examination with tubular vaginoscope, and was defined as the onset of abortion. Completion of abortion was diagnosed when no more fetuses were detected in the uterus sonographically. The clinical examinations also included inspection of the injection site for local reaction, monitoring of the bitch in terms of disturbance of general condition (anorexia and/or depression), vomiting, and diarrhea. There was examined in terms of appetite, malaise, pain, and status of injection site.

Blood sampling started in all groups before the first AGL injection, and was performed once daily until completion of abortion. Blood samples were centrifuged 3 minutes at 3500 × *g* to obtain sera. Sera samples were stored at −20 °C until analysis. Samples were analyzed for estrogen and P4 concentration. For this purpose, electrochemiluminescence immunoassay method was used (Duzen Laboratories group, Ankara, Turkey; TURKAK, TS EN ISO/IEC 17025:2005).

2.3. Statistical analyses

All statistical analyses were performed using SPSS (version 14.0 for Windows; SPSS Inc., Chicago, IL, USA). Data are given as means ± standard deviation and means ± standard error. The normality and homogeneity of variances were checked for all variables tested by means of a "Shapiro–Wilk" test and "Bartlett–Box" tests. For normally distributed data, differences between groups were compared using "one-way ANOVA." Least significant difference (LSD) *post hoc* test was performed to analyze the differences in the time interval.

The data obtained from groups were analyzed by Kolmogorov–Smirnov *Z*-test for normality of the distribution.