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USE OF AGLEPRISTONE AND AGLEPRISTONE + INTRAUTERINE ANTIBIOTIC FOR THE TREATMENT OF PYOMETRA IN BITCHES

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In this study, the efficacy of aglepristone and/or intrauterine antibiotic administration for the treatment of bitches with cystic endometrial hyperplasia/pyometra complex was investigated. Twenty-four bitches (5–12 years old) with the diagnosis of pyometra were treated at the University of Kafkas and at Istanbul University. The diagnosis of pyometra was established on the basis of the results of clinical, ultrasonographic and vaginal examinations, the haematological and biochemical findings and the history data. In Group I (n = 13), aglepristone (Antiprogestin, Alizine®, Virbac, France; 0.33 ml/kg, s.c.) was administered on days 1, 2, 7, and 14 (day 1: diagnosis). In Group II (n = 11), intrauterine antibiotic treatment was performed according to the antibiogram on days 1, 2, 4, 6, 8 in addition to aglepristone given as in Group I. Clinical and ultrasonographic examinations, haematological results and occurrence of oestrous cycles revealed that the ratio of effectively treated bitches was 6/13 and 9/11 in Groups I and II, respectively.

Key words: Bitches, pyometra, aglepristone, intrauterine

The clinical symptoms of pyometra depend on the severity and duration of the disease, existence of infection and endotoxaemia, opening of the cervical canal and the general health status (England, 1998). Pyometra with open cervical canal is characterised by haemorrhagic and mucopurulent vaginal discharge, depression, anorexia, polyuria, polydipsia and vomiting. On the other hand, pyometra with closed cervical canal is characterised by more severe clinical signs such as increase in abdominal volume, depression, anorexia, polyuria, polydipsia, vomiting and diarrhoea, and it may result in shock and even death unless proper treatment is performed (Nelson and Feldman, 1986).

Pyometra can be diagnosed by clinical examinations including clinical signs, laboratory and radiographic findings, physical examination, vaginal cytol-

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ogy and vaginal culture. Ultrasonography is also a practical tool and accurate procedure for the qualitative and quantitative examination and diagnosis of canine pyometra (Zöldág et al., 1992; Ekici et al., 1994; Baştan et al., 2003).

Pyometra is generally treated by administration of antibiotics followed by surgery; however, recently the pharmacological treatment of pyometra is acquiring greater importance. In general, oestrogens, androgens, ergot alkaloids, quinine, oxytocin and recently $PGF_{2\alpha}$ and broad-spectrum antibiotics are used for the pharmacological treatment of pyometra (Nelson and Feldman, 1986; Gilbert et al., 1989; Blendinger et al., 1997; Gábor et al., 1999; Hoffmann et al., 2000; Onclin and Verstegen, 2000). Mifepristone (RU38486), aglepristone (RU46534) and onapristone (ZK98299) are the known agents with an antiprogesterone effect (Hoffmann and Schuler, 2000). Among those drugs, aglepristone has been reported for the treatment of pyometra (Hoffmann et al., 2000).

Local infections such as metritis, pyometra, mastitis and arthritis are treated by injecting antiseptic and antibiotic solutions directly into the local infected area (intrauterine, intramammary, intraarticular) to increase their effects (Gábor et al., 1999; Noakes et al., 2001). Both pharmacological and surgical treatments have advantages and disadvantages. Side effects of prostaglandins and recurrence of pyometra are the most common. However, the risks of anaesthesia and operation in old and sick bitches and the development of stump-pyometra following improper surgery should also be taken into consideration (Harvey, 1998; Noakes et al., 2001). The objective of this study was to investigate the efficacy of aglepristone and/or administration of intrauterine antibiotics for the treatment of bitches with pyometra.

Materials and methods

This study was performed at the clinics of the Departments of Obstetrics and Gynaecology, Faculty of Veterinary Medicine, University of Kafkas and Istanbul University, between 2001 and 2003. Twenty-four bitches of different breeds and 5 to 12 years old were diagnosed as having pyometra on the basis of the results of clinical, ultrasonographic and vaginal examinations, the haematological and biochemical findings and the history data. Bitches with open (n = 13) or closed (n = 11) cervical canal had one or several of the following clinical signs: depression, anorexia, polyuria, polydipsia, vomiting, increase in abdominal volume, hyperthermia, alopecia, haemorrhagic and mucopurulent vaginal discharge. Pyometra-positive bitches were randomly assigned to one of the treatment groups based on the status of the cervical canal. In Group I (n = 13), bitches with open (n = 7) and closed (n = 6) cervical canal were treated with aglepristone (Antiprogestin, Alizine®, Virbac, France; 0.33 ml/kg; s.c.) on days 1, 2, 7, 14 (day of diagnosis: day 1). In Group II (n = 11), bitches with open (n = 6)

and closed cervical canal (n = 5) were treated with an intrauterine antibiotic based on the antibiogram results on days 1, 2, 4, 6, 8 after diagnosis in addition to aglepristone administered as in Group I. In bitches having closed-cervix pyometra the cervical canal was opened approximately 24 h after aglepristone administration; afterwards the uterine content was examined for sensitivity to different antibiotics to ensure effective treatment. Intrauterine antibiotic was administered using a newly developed, double-lined, semi-flexible, plastic catheter. This catheter was modified from a Scandinavian artificial insemination catheter for dogs (Wilson, 2001). Intrauterine antibiotic was given using this catheter through the vaginoscope. The double-lined catheter was placed into the cervix through the vaginoscope; afterwards, the inner catheter underneath of the outer catheter was inserted through the cervix and moved towards the uterine lumen to administer the antibiotic. Intrauterine antibiotic was given while the dog was laid down on her right or left side, and the caudal part of the body was elevated slightly. The bitch was kept in this position for about 10 min to allow the diffusion of the antibiotic through the uterine horns. The dosage and the dilution of the antibiotic were adjusted to the body weight and the diameter of uterine horns. The dilution rate was generally 1/5 in a total volume of 1 to 6 ml. Administration of intrauterine antibiotic is simple in dogs of large breeds due to the easy insertion of the vaginoscope and catheter compared to small breeds.

No anaesthetic was administered during intrauterine treatment with antibiotics. During the diagnosis and treatment period blood concentrations of urea and creatinine and the total red blood cell (RBC) and white blood cell (WBC) counts were determined. Furthermore, the uterus was monitored transabdominally with a real-time ultrasound machine equipped with a 5 MHz transducer. Decrease and disappearance of the vaginal discharge were checked by vaginal examination. After treatment, we periodically communicated with owners to investigate the occurrence of oestrus and mating. Clinical and reproductive examinations were performed once a week by ultrasonography both in bitches showing continuous clinical signs and in mated ones. Moreover, pregnancy was examined 25 ± 3 days after treatment. The bitches were assumed to have recovered if they did not have pyometra and/or if they showed oestrous activity. Haematological and biochemical parameters were analysed by Student's *t*-test. Recovery rates were analysed by chi-squared analyses using the Proc Freq procedure of SAS.

Results

Fifteen days after the initiation of treatment the RBC count was higher in Group II than in Group I ($P < 0.001$). In contrast, the total WBC count was lower in Group II than in Group I ($P < 0.005$). Although blood concentrations of urea and creatinine were lower in Group II than in Group I, the difference was not statistically significant (Table 1).

Table 1

Haematological and biochemical parameters (mean ± SEM) 15 days after treatment with aglepristone (Group I) and aglepristone + intrauterine antibiotic (Group II)

	Group I (mean ± SEM)	Group II (mean ± SEM)	P value
RBC count ($\times 10^9$/µl)	6.13 ± 0.27	6.91 ± 0.52	P < 0.001
Total WBC count ($\times 10^9$/l)	9179 ± 1423	7563 ± 112	P < 0.005
Urea (mg/dl)	37.12 ± 2.11	30.29 ± 4.51	NS
Creatinine (mg/dl)	1.13 ± 0.41	0.85 ± 0.03	NS

NS: not significant

Table 2

Recovery rate and percentage following treatments with aglepristone (Group I) and aglepristone + intrauterine antibiotic (Group II)

Group I (n = 13)		Group II (n = 11)	
Open (n = 7)	Closed (n = 6)	Open (n = 6)	Closed (n = 5)
5/7	1/6*	5/6	4/5*
6/13		9/11	

*Recovery rate tended to be higher in Group II than in Group I among bitches having closed-cervix pyometra (P < 0.07)

Table 3

Classification and incidence of pyometra within the groups

Group I (n = 13)						Group II (n = 11)					
Open (n = 7)			Closed (n = 6)			Open (n = 6)			Closed (n = 5)		
Case	Age	Severity	Case	Age	Severity	Case	Age	Severity	Case	Age	Severity
1	6	▲	1	8	▲▲	1	6	▲	1	7	▲
2	5	▲	2	6	▲	2	10	▲▲	2	10	▲▲▲
3	9	▲▲▲	3	5	▲	3	12	▲▲	3	11	▲▲
4	7	▲	4	10	▲▲▲	4	10	▲▲	4	7	▲
5	7	▲	5	7	▲▲	5	7	▲	5	8	▲▲
6	11	▲▲	6	12	▲▲	6	5	▲▲			
7	10	▲▲									

▲: mild pyometra; ▲▲: moderate pyometra; ▲▲▲: severe pyometra

When recovery rates were compared irrespective of whether the cervical canal was open or closed, Group II had higher recovery rates than Group I (Table 2). However, this difference was not statistically significant. Analyses of bitches with closed-cervix pyometra (n = 11) indicated that Group II had higher recovery

rate than Group I, and this difference tended to be significant ($P < 0.07$). The recovery process was more difficult and persistent in bitches with closed-cervix pyometra than in those with open-cervix pyometra in Groups I and II. The general health status of one of the bitches with closed-cervix pyometra in Group I got worse and the animal died after treatment. Fourteen out of the 24 bitches used in this study (58.3%) showed oestrous activity. Two bitches in Group I and three bitches in Group II were pregnant at the end of the study. In Group II, the ultrasonographic examination of bitches with pyometra revealed fluid-filled, anechogenic (black images) uterine lumen, and uterine horns with variable diameters and wall thickness. Pregnancies were confirmed by detecting the heartbeat of fetuses in both groups.

Data on the type, incidence and severity of pyometra in the two groups are shown in Table 3.

The antibiogram revealed that pathogenic agents present in the uterus were sensitive to amoxicillin/clavulanic acid, ampicillin/sulbactam, ciprofloxacin, enrofloxacin, erythromycin, gentamycin and lincomycin.

Discussion

It was reported that the use of aglepristone can inhibit progesterone secretion without side effects (Fieni et al., 2000; Galac et al., 2000; Hoffmann et al., 2000). Gábor et al. (1999) reported that 15 out of 17 bitches with pyometra or metritis were successfully treated by intravaginal administration of $PGF_{2\alpha}$ [150 μg/kg (0.3 ml/10 kg)] once or twice a day concomitant with a parenteral antibiotic. These researchers administered $PGF_{2\alpha}$ intravaginally to avoid any potential side effects of parenteral administration. Moreover, Gilbert et al. (1989) used $PGF_{2\alpha}$ and broad-spectrum antibiotics for the treatment of bitches ($n = 40$) with pyometra and metritis, with the following results: in 33 out of 40 bitches (82.5%) the clinical signs disappeared, 9 out of 14 bitches gave birth to puppies later, and 9 out of 20 (45%) had one or two of these complications: anoestrus, metritis, abortion. Hoffmann et al. (2000) reported that most of the bitches having pyometra returned to normal oestrus cycles, and two of them became pregnant following administration of RU 46534 (Aglepristone; 10 mg/kg; s.c.) on days 1, 2, 7 ($n = 31$) and on day 14 ($n = 1$). Likewise, Onclin and Verstegen (2000) indicated that two out of five bitches and one of two queens having pyometra were successfully treated by the oral administration of antibiotic and daily administration of aglepristone (10 mg/kg; s.c.). The results of the current study are in agreement with these reports. The results of a study on the relationship between radiographic and laboratory findings in bitches with pyometra indicated that the white blood cell count increased from $13.9 \times 10^9/1$ to $45.1 \times 10^9/1$ as the diameter of the uterus increased (Bree et al., 1988). In current study, the red

blood cell count was significantly higher ($P < 0.001$) 15 days after aglepristone and intrauterine antibiotic treatment (Group II) than after aglepristone treatment alone (Group I). However, the total WBC count was lower in Group II than in Group I ($P < 0.005$). Blood concentrations of urea and creatinine were numerically lower in Group II than in Group I, although these differences were not significant. These results suggested a quicker recovery process in Group II. In this study, the condition of the cervical canal (open or closed) affected the success rate of therapy. In this regard, the success rate of treatment for closed-cervix pyometra was numerically higher after the administration of aglepristone and intrauterine antibiotic. In contrast, the success rate of treatment of open-cervix pyometra was not affected by either treatment. The number of animals used in this study was too low to prove the importance of the open or closed position of the cervical canal in the success rate of therapy, and this question needs further research. It is not known why the recovery rate was higher following aglepristone administration and intrauterine antibiotic treatment in bitches with severe closed-cervix pyometra. It has been postulated that this combined treatment accelerated the elimination of intrauterine infection, thereby increasing the recovery rate. Aglepristone as an anti-progesterone might decrease the negative effects of progesterone on intrauterine immunity (Blendinger et al., 1997), and thus it may accelerate the elimination of intrauterine infection. However, the absence of antibiotic administration alone cannot explain the possible synergistic effect between aglepristone and antibiotic treatments. On the other hand, the higher recovery rate obtained in bitches with open-cervix pyometra compared to those with closed-cervix pyometra following anti-progesterone treatment alone suggests the necessity of intrauterine antibiotic treatment, especially in cases of closed-cervix pyometra. As the number of animals used in this study was low, it is not possible to establish any relationship between the recovery rate and the age or severity of the cases.

In conclusion, it can be established that aglepristone can be used safely for the treatment of pyometra irrespective of whether the cervical canal is open or closed.

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