TREATMENT OF PYOMETRA IN FEMALE DOGS USING PROSTAGLANDIN $F_{2\alpha}$ ± ANTIPROGESTIN (MIFEPRISTONE)

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ABSTRACT

The female dogs confirmed for pyometra by history, clinical examination, ultrasonography and blood sampling were subjected to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) therapy with or without mifepristone, an antiprogestin (n=6 in each group). Following treatment, 11 out of 12 animals were successfully treated and recurrence till next estrous cycle was observed only in one case. The clinical signs uterine diameter and hemato-biochemical parameters were normalized by day 14 post onset of treatment in both the groups ($p<0.05$). By day 7, plasma progesterone decreased ($p<0.05$) in group receiving $PGF_{2\alpha}$ alone, but increased in group receiving antiprogestin plus $PGF_{2\alpha}$. Briefly, mifepristone appears to be a safe and promising option for opening the cervical canal in closed pyometra cases of dogs and if used in combination with $PGF_{2\alpha}$, a success rate of upto 100% for the treatment of either type of pyometra can be expected in the absence of ovarian cysts.

Keywords: Canine, Dog, Mifepristone, $PGF_{2\alpha}$, Pyometra

INTRODUCTION

Canine pyometra is a diestrual disease and the use of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) for the treatment of open pyometra is widely accepted (Feldman and Nelson, 1996). Progesterone blockers suggested to be of special interest for closed pyometra treatment in canines (Fieni, 2006). In fact, the use of an antiprogestin (aglepristone) in combination with $PGF_{2\alpha}$ was highly successful (Fieni, 2006). But the availability of aglepristone is limited to some countries. Another antiprogestin namely mifepristone has been used for termination of pregnancy and induction of whelping in canines (Concannon *et al*., 1990 and Reddy *et al.,* 2012). The present study was planned to evaluate the efficacy of mifepristone in combination with $PGF_{2\alpha}$ as compared to $PGF_{2\alpha}$ alone for the treatment of canine pyometra.

MATERIALS AND METHODS

Twelve female dogs (age: 6-12 yr) with suspected pyometra based upon the history of diestrus and clinical signs of inappetance, lethargy, polyuria, polydypsia and vulvar discharge (if present) were confirmed for pyometra by 5-6.5 MHz curvilinear transducer aided ultrasonographic examination. In a group (n=6) of animals with open pyometra, dinoprost tromethamine (a natural $PGF_{2\alpha}$) was administered (s.c.) in a progressively increasing dose @ 50-200 ìg/kg from day 1 to 5 (d1, 50 ìg/kg; d2, 100 ìg/kg; d3, 150 ìg/kg; d4 and d5, 200 ìg/kg). In group II dogs (4 with open and 2 with closed pyometra), mifepristone was administered orally @ 2.5 mg/kg on day 1, 2 and 8 along with dinoprost tromethamine (s.c.) in a progressively increasing dose @ 50-200 ìg/kg from day 3 to 7. The owners were informed about side effects of $PGF_{2\alpha}$ treatment and $PGF_{2\alpha}$ was administered at about 4 h difference from feeding time and the animals were kept under observation for 20 minutes.

Irrespective of treatment group, a four-quadrant antibiotherapy (without performing culture sensitivity test) was instituted after definitive diagnosis. Enrofloxacin @ 5 mg/kg s.i.d. for 5-7 days plus amoxicillin-dicloxacillin

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or amoxicillin-clavulanate @ 14 mg/kg b. wt. b.i.d. for 7 to 30 days was prescribed depending on the change in the nature of discharge and/or uterine evacuation as assessed by ultrasonography. Also, a supportive therapy in form of intravenous fluids and multi-vitamins was administered as and when required.

Following start of treatment, the animals were daily examined clinically to evaluate treatment response in terms of activity, appetite and vulvar discharge. The assessment of uterine distention was confirmed by follow-up ultrasonography on day 7 and 14 and, if required, on day 21 and 30. The blood samples were collected on day 1 (before administering treatment) and on days 7 and 14. Various Hemato-biochemical parameters were estimated by standard methods (Table). Plasma progesterone estimation was done by liquid phase radioimmunoassay (Ghuman *et al.,* 2009). The statistical analysis was done by Student's t-test using SPSS 16.0 software.

RESULTS AND DISCUSSION

In present study, the overall response to treatment was successful in 11 out of 12 female dogs. At the start of treatment, uterine diameters in female dogs ranged from 1.7 to 4.2 cm that decreased to d"1cm on day 14 post-treatment onset in all the animals irrespective of treatment group, except an open pyometric animal (Mifepristone + $PGF_{2\alpha}$) which showed incomplete evacuation, thus, ovariohysterectomy was performed and ovarian cysts were detected. In previous studies also, a, failure to medical treatment of pyometra was observed in presence of ovarian cysts (Trasch *et al.*, 2003 and Fieni, 2006).

Nevertheless, the success of treatment was associated with improved activity and appetite as well as an initial increase in vulvar discharge followed by diminished and serous nature of discharge. In all the treated animals, vulvar discharge increased within 24-48 h after the start of treatment with an improvement in their general clinical condition. The uterotonic effect of $PGF_{2\alpha}$ might have led to successful evacuation of uterus in these animals. Two cases of closed-cervix pyometra became open after 36-48 h of onset of mifepristone therapy as evidenced by the onset of vulvar discharge. In these cases, the removal of inhibitory effect of progesterone on uterine contractions by mifepristone treatment may have opened cervical canal and subsequently, the ecbolic effect of $PGF_{2\alpha}$ could have contributed to uterine evacuation. Mifepristone has five times greater relative binding affinity than progesterone for progesterone receptors (Philibert *et al*., 1985), thus, mimicing the effects observed during luteolysis and leading to relaxation of cervix (Verstegen *et al.,* 2008).

The impairment of renal function along with other multiple organ dysfunctions is a frequent complication of pyometra (Heine *et al.,* 2007). Therefore, in the present study, the haemato-biochemical indices were altered at the start of treatment (leukocytosis, neutrophilia, azotemia and elevated ALP in >50% bitches); however, these indices were almost normal by day 14 post-treatment onset in both the groups (Table). This reversal of toxemia was consistent with other studies (Verstegen *et al.,* 2008).

The repeated administration of $PGF_{2\alpha}$ in canines is known to cause luteolysis and reduction in plasma progesterone (Pande *et al*., 2011). Similar findings were reported following $PGF_{2\alpha}$ treatment alone as plasma progesterone declined on day 7 and 14 post-treatment compared to initial levels ($p<0.05$, Table). However, an initial rise in plasma progesterone was observed on day 7 post-treatment in the mifepristone plus $PGF_{2\alpha}$ treatment group ($p>0.05$, Table). This could be explained by the blocking of uterine progesterone receptors by mifepristone and the consequent elevation of circulating progesterone (Gobello *et al*., 2003).

In the present study, recurrence of pyometra till next estrous cycle was observed only in one animal. Previously, a recurrence rate of 9.8-20% was observed in successfully treated pyometric dogs (Trasch *et al*., 2003 and Gobello *et al*., 2003).

Table: Hemato-biochemical parameters and plasma progesterone in pyometric female dogs undergoing prostaglandin therapy with or without mifepristone (Gp I, $PGF_{2\alpha}$; Gp II, Mifepristone+$PGF_{2\alpha}$)

Parameters	Group	Day 1	Day 7	Day 14
TLC, $10^3/mm^3$	Gp I	21.75 ± 1.65^{a}	11.00 ± 1.08^{b}	8.50 ± 0.64^{b}
	Gp II	20.00 ± 1.47^{a}	10.50 ± 0.64^{b}	8.75 ± 0.47^{c}
Neutrophils, %	Gp I	79.00 ± 1.08^{a}	67.50 ± 0.65^{b}	66.00 ± 0.41^{b}
	Gp II	78.00 ± 0.71^{a}	68.75 ± 0.85^{b}	67.25 ± 0.63^{c}
BUN, mg/dl	Gp I	46.69 ± 1.43^{a}	$34.39\pm0.80^{b,x}$	23.72 ± 1.75^{c}
	Gp II	46.01 ± 3.29^{a}	$28.20\pm1.28^{b,y}$	16.54 ± 1.89^{c}
Creatinine, mg/dl	Gp I	2.53 ± 0.31^{a}	1.61 ± 0.24^{b}	1.00 ± 0.05^{b}
	Gp II	2.56 ± 0.36^{a}	1.60 ± 0.32^{b}	0.94 ± 0.03^{b}
AST, IU/L	Gp I	60.59 ± 3.37^{a}	48.63 ± 4.59^{b}	36.73 ± 2.49^{b}
	Gp II	59.34 ± 4.19^{a}	48.21 ± 2.43^{b}	38.93 ± 1.61^{c}
ALP, IU/L	Gp I	$156.9\pm10.6^{a,x}$	113.6 ± 8.8^{b}	70.28 ± 8.88^{c}
	Gp II	$117.3\pm16.5^{a,y}$	98.3 ± 9.9^{a}	64.29 ± 5.85^{b}
Progesterone, ng/ml	Gp I	2.01 ± 0.70^{a}	1.27 ± 0.55^{b}	1.00 ± 0.41^{b}
	Gp II	1.82 ± 0.55^{a}	2.15 ± 0.66^{a}	1.13 ± 0.71^{a}

$^{a,b,c}p<0.05$, within a row; $^{x,y}p<0.05$, for a parameter within a column, TLC, Total leucocyte count; BUN, Blood urea nitrogen; AST, Aspartate aminotransferase; ALT, Alkaline phosphatase; Day 1, Before start of treatment

In brief, mifepristone proves to be safe and efficient drug for opening the cervical canal in dogs with closed pyometra. Its use in combination with $PGF_{2\alpha}$ emerges new therapeutic possibilities with a high success rate for the treatment of either type of pyometra.

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