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Comparison of the Use of Cephapirin and Oxytetracycline for the Treatment of Clinical Endometritis in the Camel (*Camelus dromedarius*): A Field Study

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Abstract: This study compared the use of cephapirin and oxytetracycline for the treatment of clinical endometritis in the camel (*Camelus dromedarius*). Sixty multiparous camels suffered from repeat breeding during the breeding season and were owned by Bedouin in Riyadh, Saudi Arabia were included in this study. The perineal region of the camels was inspected for the presence of any discharge and the animals underwent rectal and vaginal palpation. Additionally, trans-rectal ultrasound examinations were performed to examine the reproductive organs, the thickness of the uterine wall and the uterine contents. Forty eight camels were diagnosed with endometritis and randomly assigned to one of two groups. All camels in both groups were treated with a single intra-uterine dose of antibiotic during their estrus phase. In group A, camels were infused with 500 mg of cephapirin benzathine (Metricure®). In group B, camels were treated with 2 g of oxytetracycline HCl (Tetravet Foaming Pessary®). About 14 days after the intra-uterine treatment, all camels were re examined ultrasonographically to evaluate their response to treatment. Only recovered camels were allowed to mate naturally 3 weeks after intra-uterine treatment. Pregnancy was diagnosed ultrasonographically on day 20 post-mating and confirmed on day 40. The recovery was significantly higher ($p<0.01$) in cephapirin-treated animals (87.5%) than in oxytetracycline-treated animals (66.7%). Moreover, the conception rate was significantly higher ($p<0.01$) in camels treated with cephapirin (76.2%) than in camels treated with oxytetracycline (62.5%). In conclusion, cephapirin can be considered an efficient intra-uterine antibiotic for the treatment of endometritis in camels. Additionally, cephapirin produces better post-treatment conception rates than oxytetracycline.

Key words: Cephapirin, oxytetracycline, endometritis, camel, ultrasonographically

INTRODUCTION

The camel is an important animal in many areas of the world, especially in Saudi Arabia. The total population of dromedaries consists of approximately 1.6 million animals within the Arabian Peninsula, 53% of which are found in Saudi Arabia. Saudis and Bedouins prefer camel meat and milk to other types of meats and milks. Camel meat is considered to be superior to and healthier than other types of meat because of its higher protein and lower fat content it is recommended for the prevention of cardiovascular disease and atherosclerosis because it lowers cholesterol levels in the blood. Camel meat may protect against tumors because it contains unsaturated fatty acids such as linoleic acid. Camel meat can also be used to cure exhaustion and fatigue because it contains more glycogen than other types of meat (Kadim *et al*., 2008). Camel milk is considered to be a complete food source that can sustain a person through a typical day. It maintains its quality and texture for 12 days and is a rich source of proteins with potential antimicrobial activities that are not found or found only in small amounts in other types of milk. Camel milk is lower in lactose, short-chain fatty acids and cholesterol but higher in water (89.6%), prolactin, vitamins (especially C and B1), volatile acids (especially linoleic and polyunsaturated), minerals (potassium, magnesium, iron, copper, manganese, sodium and zinc) and immunoglobulins than other types of milk (Morton, 1984; Wernery, 2007).

Despite the above-mentioned benefits of camel meat and milk, camel production is still not undertaken on a commercial scale. The reproductive efficiency of dromedary camels is generally considered to be low. Birthing rates rarely exceed 40% in nomadic herds or 70% in more intensive herds (Tibary and Anouassi 1997a; Tibary *et al*., 2005; Kaufmann, 2005). Uterine inflammation

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results in diminished fertility and is a considerable barrier to camel production often resulting in significant economic loss. Uterine inflammation has been described as the most commonly encountered form of infertility in dromedary camels (Tibary and Anouassi, 2000). Inadequate clinical trials comparing the efficacy of different treatments for endometritis have been performed in the camel. Additionally, the efficacy of antibiotics should be evaluated periodically because resistant strains of bacteria can arise owing to the indiscriminate use of antibiotics (Vekateswaran and Rajeswar, 1991). Most veterinarians treat camels with treatments that are traditionally used for the treatment of bovine or equine endometritis including uterine flushing, intrauterine antibiotic infusion, systemic antibiotic treatment or a combination of the above methods. Intrauterine antibiotic therapy has been preferred over systemic therapy because of the assumption that reservoirs of bacteria are located within the uterine lumen and antibiotics administered directly to the uterus reach higher inhibitory concentrations than systemically administered antibiotics (LeBlanc, 2009). For an intrauterine antibiotic to be successful, it should be effective against the pathogens present, not inhibit the uterine defense mechanisms be effective in a pyogenic environment, leave no residues in milk or meat be administered at an adequate concentration and with an adequate number of treatments and be cost-effective.

Cephapirin, a first generation cephalosporin and oxytetracycline satisfy most of the criteria for the treatment of endometritis (Noakes *et al*., 1991). They are both broad-spectrum antibiotics with bactericidal action against Gram-positive and Gram-negative bacteria in addition they are both resistant to the action of penicillinase and active in an anaerobic environment. Oxytetracycline is poorly absorbed in the uterus after an intrauterine infusion (Bretzlaff *et al*., 1983) though it achieves higher more long-lasting levels in the endometrium than if it had been administered by other injection routes (Masera *et al*., 1980). Oxytetracycline can be an irritant thus it stimulates the inflammatory response and uterine defensive reactions and promotes Polymorphonuclear leukocytes (PMN) infiltration to the uterine lumen and the regeneration of uterine tissue. Therefore, it can be a very useful antibiotic for the treatment of endometritis, especially in cases of chronic endometritis. Nevertheless, it is not used by certain practitioners because it leaves residues in the milk. In contrast, cephapirin leaves no residue in milk and it achieves concentrations in the endometrial tissue above the Minimal Inhibitory Concentration (MIC) of sensitive bacteria for at least 24 h after a single treatment (Adams, 2001). The present study sought to evaluate the efficacy of a single intrauterine infusion of cephapirin or oxytetracycline for the treatment of endometritis in camels and to assess the effect of these antibiotics on post-treatment conception rates.

MATERIALS AND METHODS

Animals: Sixty multiparous 7-10 years old camels (*Camelus dromedarius*) were included in the present study. The animals were owned by Bedouins in Riyadh, Saudi Arabia. All camels were generally healthy with no systemic signs of illness. Bedouins complained of the necessity for repeat breeding of these camels and reported that their animals were bred more than three times to different fertile males in three different estrus cycles during the breeding season without achieving conception.

Gynaecological examinations: All camels were subjected to reproductive examination including external and internal examination. An external examination was performed for the vulva, perineum and base of the tail to detect any abnormal discharge or dried flakes. Internal examinations including rectal palpation, ultrasonography (WED-2000 Portable Ultrasound Scanner, VED, Guangdong, China) and vaginal exploration were performed. The presence of abnormal uterine content, increased uterine size and increased thickness of the uterine wall were noted.

Treatment regimes: Forty eight camels were diagnosed with clinical endometritis, randomly assigned to one of two equal groups and treated with a single intra-uterine dose of antibiotic during the heat phase. In group A, camels were infused with 500 mg of cephapirin benzathine (Metricure®; Intervet Ltd. Netherlands). In group B, camels were treated with 2 g of oxytetracycline HCl (Tetravet Foaming Pessary, Bomac Laboratories Ltd. New Zealand). For logistical reasons, researchers eated diseased group in this study. However, the reproductive performance of the healthy control group can be regarded as the gold standard (Drillich *et al*., 2005).

Assessment of recovery response: About 14 days after the intra-uterine treatment, all camels were re-examined ultrasonographically to evaluate their recovery. Only recovered camels were allowed to mate naturally 3 weeks after receiving the intra-uterine treatment. Minimum contamination breeding technique was used via the

ultrasonographic monitoring of ovarian activity, animals were bred only once the follicle was mature (12-18 mm) and ovulation was induced using 0.021 mg of buserelin acetate (5 mL Receptal®, Intervet/Schering-Plough Animal Health). Pregnancy was diagnosed by ultrasonography on day 20 post-mating and confirmed on day 40.

Statistical analysis: Data were analyzed to determine the effects of clinical endometritis treatment by cephapirin vs. oxytetracycline HCl on the recovery and pregnancy rate of dromedary camels. The differences in the percentages achieved in each treatment group were evaluated by the χ^2-test. The level of significance was tested at a 1% level of probability. The SPSS Statistical Program was used to perform the Statistical Analyses (SPSS, 2007).

RESULTS AND DISCUSSION

Uterine infections represent one of the major complaints in camelid veterinary medicine. Sixty animals that had repeat breeding, forty eight (80%) camels were diagnosed with clinical endometritis. In the present study, the recovery was significantly higher ($p<0.01$) for animals treated with cephapirin (21/24, 87.5%) than for those treated with oxytetracycline (16/24, 66.7%). Moreover, the pregnancy rate was significantly higher ($p<0.01$) in camels treated with cephapirin (16/21, 76.2%) than in camels treated with oxytetracycline (10/16, 62.5%) (Table 1).

Poor reproductive efficiency is a major problem in camelids. The reproductive rate in camelids varies from 25-80% depending on the management and level of veterinary care provided (Tibary and Anouassi, 1997a). Various uterine disorders have been described and may play an important role in the reduced fertility observed in camels (Tibary and Anouassi, 1997b). Similar to many domestic animal species, uterine infections are the most commonly acquired reproductive problems that result in infertility in camels (Wernery and Kumar, 1994; Tibary *et al*., 2001; Aly *et al*., 2010). The major contributing factors to this condition are over-breeding, postpartum complications and unsanitary gynecological manipulations (Tibary, 2004). A uterine infection should be suspected in any animal with a history of repeat breeding or early embryonic death and can be confirmed by clinical examination; manual vaginal examination can also be used to diagnose uterine infection and is likely more practical and simpler than a complete clinical examination (Sheldon *et al*., 2002). The sub-fertility associated with uterine infections is caused by uterine damage and the disruption of ovarian function (Sheldon and Dobson, 2004). The results of this study revealed that 48 of 60 camels (80%) examined for repeat breeding were diagnosed with clinical endometritis.

Table 1: The recovery response and pregnancy rate of she-camels treated from endometritis using cephapirin or oxytetracycline

Treatments	Cephapirin	Oxytetracycline	Total number
No. of recovered and bred she-camels (%)	21 (87.5%)*	16 (66.7%)	37 (77.1%)
No. pregnant she-camels (%)	16 (76.2%)*	10 (62.5%)	26 (70.3%)

*Significant at $p<0.01$

The efficacy of the endometritis treatment depends on the type of antibiotic used the volume and frequency of infusion, the causative bacteria and the duration and degree of endometrial changes. The most common bacteria isolated from the uterus of camelids with endometritis were *Escherichia coli*, *Streptococcus zooepidemicus*, beta hemolytic Streptococci, *Enterococcus* sp., coagulase-negative Staphylococcus, *Proteus* sp., *Enterobacter aerogenes*, *Klebsiella pneumoniae* and *Arcanobacterium pyogenes* (Wernery and Kumar, 1994; Chauhan *et al*., 1987; Enany *et al*., 1990; Nawito, 1973; Wernery, 2007; Wernery and Wernery, 1992). Because of the wide variety of bacteria that can cause uterine infections, veterinarians must either use broad-spectrum antibiotics or obtain bacterial cultures and carry out sensitivity tests to determine the most appropriate antibiotic for treating endometritis. However, most of these organisms are ubiquitous which makes uterine culture results misleading if they are not interpreted correctly and correlated with clinical findings.

The uterus is an anaerobic environment thus antibiotics chosen for intrauterine use must be active in the absence of oxygen (El-Azab *et al*., 1988). In addition, because most antibiotics and chemicals depress the activity of uterine neutrophils and interfere with uterine defense mechanisms, the potential benefits of their use must be carefully weighed against the potential deleterious effects (Vandeplassche, 1981). Organisms that cause uterine infections are usually sensitive to penicillin but bacterial contamination can produce penicillinase which renders the drug ineffective if applied locally.

In the present study, recovery was significantly more frequent ($p<0.01$) in cephapirin-treated animals (87.5%) than in oxytetracycline-treated animals (66.7%). This result is in agreement with the results of other researchers who reported that intrauterine infusions of cephapirin benzathine (Metricure®) improved the reproductive performance of cows with subclinical endometritis (diagnostic criteria: >18% PMNs using endometrial cytobrush cytology) (30-33). Kasimanickam *et al*. (2005) reported that cows with subclinical endometritis that received cephapirin between 20 and 33 days in milk experienced an 89% increase in pregnancy rate compared

with non-treated cows. Dohmen *et al.* (1995) reported that intrauterine infusions of cephapirin resulted in an 80% clinical cure rate and 60% bacterial clearance rate within 2 weeks of treatment. LeBlanc (2008) showed that using cephapirin in cows 27 and 33 days postpartum resulted in a 60% higher likelihood of those cows becoming pregnant and a 29% reduction in time to pregnancy compared with their untreated herd mates. McDougall (2003) reported that cows treated with cephapirin at 41±14 DIM were approximately 2-3 times more likely to be pregnant by 56 days than untreated cattle; he concluded that intrauterine treatments with 0.5 g of cephapirin improved the reproductive performance of dairy cattle.

Cephalosporins are commonly used in both human and veterinary medicine (Hornish and Kotarski, 2002). Cephapirin is a first generation cephalosporin and a broad-spectrum antibiotic with bactericidal action against Gram-positive and Gram-negative bacteria. Cephapirin is resistant to the action of penicillinase and is active in an anaerobic environment such as an infected uterus (Adams, 2001). Cephalosporin has been recommended as an alternative drug for patients who do not appear to respond to penicillin (Kasimanickam *et al.*, 2005; Youngquist, 1997). Cephalosporins, like penicillins, interfere with bacterial cell wall synthesis, particularly with the terminal stages of peptidoglycan synthesis of cells in the growth phase: an alteration in cell wall permeability allows the entry of water into the cell and produces cell death. Because the cell wall is specific to the prokaryotic cell, this antimicrobial activity does not interfere with mammalian cells, a key advantage of using an antibacterial agent in the therapy of endometritis. After a single treatment with Metricure®, concentrations of cephapirin above the MIC of sensitive bacteria are maintained in endometrial tissue for at least 24 h. The suspension is well tolerated, enables good diffusion of cephapirin into the endometrium and is easily infused. The residue data and use pattern support a 2 days withholding period for meat and a NIL withholding period for milk (Adams, 2001). Therefore, cephapirin may be a good choice for the treatment of uterine infections in dairy animals.

Oxytetracycline is a broad-spectrum antibiotic that is active in mucopurulent and anaerobic environments. Its irritating nature causes an inflammatory response, stimulates the defensive reaction of the uterus, promotes PMN infiltration to the lumen of the uterus and stimulates the regeneration of uterine tissue. Therefore, it can be a very useful antibiotic for the treatment of endometritis especially in cases of chronic endometritis. Oxytetracycline was the most popular agent used to treat endometritis many years ago. When antimicrobial therapy is indicated, oxytetracycline is recommended for intrauterine use when mixed bacterial populations are present (Bretzlaff, 1987). It satisfies most of the criteria for the treatment of endometritis: it is poorly absorbed in the deeper layers of the uterus (Bretzlaff *et al.*, 1983, Bretzlaff, 1987) and it achieves higher and longer-lasting endometrial concentrations when infused than it would if administered by other parenteral routes (Masera *et al.*, 1980). Oxytetracycline concentrations are high enough in the caruncles and the endometrium 24 h after an intrauterine infusion of 5.5 mg kg^{-1} but insufficient in the myometrium and ovaries (Bretzlaff, 1987; Scheldon and Noakes, 1998). Scheldon and Noakes (1998) reported that the cure rate of postpartum endometritis using oxytetracycline, cloprostenol and estradiol were 73, 67 and 63%, respectively. Significantly higher success rates were achieved for the treatments of cows with mild endometritis with oxytetracycline than with estradiol. The conception interval was also shorter in cows treated with oxytetracycline and PGF2α than in cows treated with estradiol.

Although, oxytetracycline is widely used, Cohen *et al.* (1996) demonstrated that the intrauterine infusion of this drug may be inappropriate because of the lack of sensitivity of the bacteria causing the infection. Most isolates of *Actinomyces pyogenes* recovered from the uterus of cows were resistant to oxytetracycline and intrauterine treatments with large doses of this antibiotic did not affect the frequency of *A. pyogenes* isolation. Sheldon *et al.* (2004) showed that oxytetracycline achieved the highest MIC values of all antibiotics frequently used to treat uterine infections including cephapirin. Additionally, many preparations of oxytetracycline are irritating and cause chemical endometritis. Furthermore, the meat and milk residues discourage certain practitioners from using oxytetracycline. The absorption of this drug from the uterus to the peripheral blood occurs within 12 h. Using the tetrazolium chloride assay, a single treatment was found to produce residue in milk for 1-8 days and the period tended to be longer in cows that had received more than one dose (Tan *et al.*, 2007).

In the present study, the conception rate was significantly higher ($p<0.01$) in camels treated with cephapirin (76.2%) than in camels treated with oxytetracycline (62.5%). Pregnancy rates in camelids treated for endometritis range from 30-60% (Wernery and Kumar, 1994; Powers *et al.*, 1990). In another study, the conception rates obtained after endometritis treatment with acriflavine 0.1%, lotagen 4% and gentamicin (300 mg 100 mL^{-1}) were 58.9, 49.3 and 42.5%, respectively (Aly *et al.*, 2010).

CONCLUSION

Cephapirin can be considered a good intra-uterine antibiotic for the treatment of endometritis in camels. Additionally, cephapirin produces better post-treatment conception rates than oxytetracycline.

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