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Efficacy of single-dose ceftriaxone versus multiple-dose enrofloxacin in dogs with uncomplicated lower urinary tract infection: a randomised clinical trial

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ABSTRACT: Dogs with uncomplicated lower urinary tract infection (LUTI) are usually treated with appropriate antibiotics for 10–14 days. In humans, a single dose of ceftriaxone is employed in the treatment of uncomplicated LUTI. The purpose of the current study was to compare the efficacy of a single dose of ceftriaxone with multiple dose (14 days) enrofloxacin administration in dogs with uncomplicated LUTI. Forty-seven non-pregnant client-owned dogs with LUTI signs were enrolled in this prospective, controlled, randomised, blinded clinical trial. The inclusion criteria were the presence of at least one type of bacteria greater than or equal to 1000 CFU/ml in each urine sample. Dogs were assigned randomly to Group ENR (n = 23) enrofloxacin treatment (5 mg/kg, *s.c.*, *s.i.d.*, for 14 days) and Group CEF (n = 20) ceftriaxone treatment (25 mg/kg, *i.v.*, once). The time needed for disappearance of clinical signs ranged from 4–9 days and 1–5 days for Group ENR and Group CEF, respectively. Clinical signs significantly improved earlier in Group CEF than in Group ENR ($P < 0.0001$). Urine culture with less than or equal to 1000 CFU/ml was achieved on Days 17–21 after the first day of treatment in all dogs. Although a single dose of ceftriaxone can be considered as an alternative treatment to alleviate the signs of uncomplicated LUTI in dogs, its status as drug of last resort is a limiting factor for its extensive use in clinical practice.

Keywords: antibiotherapy; canine; haematuria; stranguria; urine

About 14% of dogs suffer from a urinary tract infection during their lifetime (Ettinger and Feldman 2010). Development of uncomplicated lower urinary tract infections (LUTIs) is associated with transient disruption of host defence mechanisms that prevent microorganisms from adhering within the urinary tract (Ball et al. 2008; Ettinger and Feldman 2010; Chew et al. 2011). The choice of appropriate antibiotics for the treatment of urinary tract infections depends on their ability to accumulate at concentrations that exert therapeutic effects. Resistance status and spectrum, the side effects of an antimicrobial agent and the duration of therapy all play a significant role in the choice of antibiotics for effective treatment of urinary tract infections (Nicholle 2002). Traditional treatment of canine uncomplicated LUTIs involves administration of an appropriate antimicrobial agent for 10–14 days (Ettinger and Feldman 2010; Weese 2011). Studies dealing with the consequences of widespread administration of enrofloxacin have demonstrated an increase in the proportion of resistant bacteria isolated from dogs with urinary tract infections (Cooke 2002; Cohn 2003). Ceftriaxone therapy has been documented to be efficacious in the management of human complicated or uncomplicated urinary tract infections (Iravani and Richard 1985; Park et al. 2012; Lin et al. 2016). However, pharmacological studies investigating the efficacy of ceftriaxone in veterinary medicine are limited (Soback and Ziv 1988; Ringger et al. 1996; Ringger et al. 1998; Rebuelto et al. 2002). Although ceftri-

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axone is a third generation and broad spectrum cephalosporin which is regarded as a drug of last resort rather than first-line therapy, this study was conducted to compare the efficacy of a single dose of ceftriaxone with multiple doses of enrofloxacin in the treatment of uncomplicated LUTIs in dogs. It was hypothesised that the clinical success of ceftriaxone administration would be similar to that of enrofloxacin administration in dogs with LUTI.

MATERIAL AND METHODS

Study population. The study population consisted of 47 non-pregnant client-owned dogs referred to the Small Animal Hospital with complaints of LUTI signs including macroscopic haematuria, stranguria (dysuria), pollakuria or licking of the genital area. Dogs did not receive any medication at the time of referral and during diagnostic applications. The inclusion criterion was the presence of at least one type of bacteria greater than or equal to 1000 CFU/ml in each urine sample (Bartges 2004; Ettinger and Feldman 2010). Dogs were excluded from the study if they had obstructive, prostatic, or congenital urinary tract diseases. Dogs that had antimicrobial resistance to enrofloxacin or ceftriaxone (all isolates were susceptible to the given drugs), that had received drug therapy (including antibiotics) within the preceding seven days, that had impaired renal and liver function and concurrent disease such as diabetes mellitus and hyperadrenocorticism, or that exhibited signs of complicated urinary tract disease in history, clinical examination and routine blood analysis (CBC and biochemical profile), were also excluded from the study. Based on these inclusion and exclusion criteria, a total of 43 dogs were finally included in the study.

Experimental design. In this prospective randomised trial, all dogs were examined by a standardised protocol including clinical examination, routine blood analysis, diagnostic imaging (abdominal radiographs and ultrasonography), dipstick urinalysis, and urine culture. Urine samples were obtained by ultrasound-guided cystocentesis not more than one hour prior to laboratory examinations. Clipping and aseptic technique were also employed before collecting urine samples. All samples were inoculated on Urinary Tract Infections Chromogenic Agar (Oxoid Limited, Hampshire, England) and Eosin Methylene Blue Agar (Oxoid Limited, Hampshire, England) using a standard bacteriological technique with a 1-µl loop and incubated at 37 °C overnight. Identification and antimicrobial susceptibility testing of urinary pathogens were performed at the same laboratory (a government-accredited facility) using the Matrix Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry System (Biomerieux S.A. Marcy l'Etoile, France). Pathogens were recorded as being either sensitive or resistant to enrofloxacin and ceftriaxone. Urine specific gravity and pH were measured using dipstick tests (Urit 50 Urine Analyzer, Guangxi, Chine).

In order to achieve statistical significance for any shortening of the time needed for the improvement of symptoms, sample size per group was calculated to be 18 with an alpha error (type I) of 0.05 and power of 0.90 (beta error, type II). Computer-generated randomisation was used to assign the dogs into Group ENR (n = 23): enrofloxacin (Baytril-K %5, Bayer Healthcare, USA) treatment (5 mg/kg, *s.c.*, *s.i.d.*) for 14 days and Group CEF (n = 20): ceftriaxone (Rocephin, Roche, Switzerland) treatment (25 mg/kg, *i.v.*) once. All injections were given between 8.30 a.m. and 10.00 a.m. Clinical response times to elimination of macroscopic haematuria, stranguria (dysuria), pollakuria, and licking of the genital area in hospitalised dogs were daily evaluated by an investigator who was blind to the treatments. Negative urine culture or results with values of less than or equal to 1000 CFU/ml obtained on Days 17–21 after the first day of treatment were defined as "microbiological cure", whereas complete disappearance of the clinical signs in response to treatment was denoted as "clinical cure".

Statistical analysis. Commercial statistical software was used for data analyses (SAS 2002, v. 9, SAS Inst., Inc., Cary, USA). Association of breed and sex with presence of macroscopic haematuria, stranguria (dysuria), pollakuria, and licking the genital area (discrete variables) were attained by the chi-squared test using the Proc FREQ and TABLE procedures. The continuous urine parameters (specific gravity and pH) between groups were compared with Student's t-test using the Proc MEANS procedure after ensuring normality using the Kolmogorov-Smirnov test (the Proc. NPAR1WAY procedure). The effect of treatments on the time required for a decrease in clinical signs was determined by one-way ANOVA using the Proc GLM procedure. Statistical significance was declared at $P < 0.05$.

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RESULTS

Pre-treatment clinical and bacteriological findings

Data were collected from 47 dogs (Highland white terrier, *n* = 3; Yorkshire terrier, *n* = 2; Cairn terrier, *n* = 1; Kangal, *n* = 3; Boxer, *n* = 3; Miniature pinscher, *n* = 5; German shepherd, *n* = 4; Mongrel, *n* = 11; Doberman pinscher, *n* = 2; Beagle, *n* = 2; Pointer, *n* = 2; Golden retriever, *n* = 1; and Rottweiler, *n* = 8). Four dogs were excluded from the study because of urolithiasis (Yorkshire terrier, *n* = 1), impaired renal function and fever greater than 39.3 °C (German shepherd, *n* = 1; Beagle, *n* = 1), and benign prostatic hyperplasia (Golden retriever, *n* = 1). The mean age ($P < 0.72$) as well as gender ($P < 0.23$) and breed ($P < 0.51$) distributions of dogs did not vary by the treatment group (Table 1). In both groups, *E. coli* was the predominant agent causing uncomplicated LUTI (Table 1).

Table 1. Distribution of dog characteristics and uropathogens causing LUTIs in the two treatment groups. Dogs were administered enrofloxacin (5 mg/kg, *s.c.*, *s.i.d.*) for 14 days (Group ENR, 12 females and 11 males, 3.37 ± 0.37 years) or a single dose of ceftriaxone (25 mg/kg, *i.v.*, Group CEF, 14 females and six males, 3.55 ± 0.36 years)

	Breed (*n*)	Pathogen (*n*; %)
Group ENR	Beagle (1)	*Escherichia coli* (10; 43.5)
	Boxer (1)	*Staphylococcus* spp. (5; 21.7)
	German shepherd (3)	*Enterococcus* spp. (6; 26.1)
	Kangal (1)	*Klebsiella* spp.(2; 8.7)
	Miniature pincher (2)	
	Mongrel (7)	
	Pointer (1)	
	Rottweiler (5)	
	Yorkshire terrier (1)	
	Cairn terrier (1)	
Group CEF	Boxer (2)	*Escherichia coli* (9; 45.0)
	Doberman pincher (2)	*Staphylococcus* spp. (8; 40.0)
	Kangal (2)	*Proteus* spp.(3; 15.0)
	Miniature pincher (3)	
	Mongrel (4)	
	Pointer (1)	
	Rottweiler (3)	
	Highland white terrier (3)	

The incidence of clinical signs related to uncomplicated LUTI, including haematuria, stanguria (dysuria), pollakuria as well as behaviour (licking the genital area) prior to the experiment were similar between the treatment groups (Table 2). Pre-treatment urine parameters were not different. The mean urine specific gravity and urine pH were 1.024 ± 0.001 (range, 1.010–1.030) and 7.175 ± 0.236 (5.0–9.0), respectively (Table 2).

Clinical and bacteriological response

Table 3 summarises the effect of administration of enrofloxacin (5 mg/kg, *s.c.*, *s.i.d.*) for 14 days or a single dose of ceftriaxone on days needed to achieve clinical remission in dogs with uncomplicated LUTI. The time needed for the disappearance of clinical signs following treatment ranged from 4–9 days vs 1–5 days in Group ENR and Group CEF, respectively. Signs, including macroscopic haematuria, stranguria (dysuria), pollakuria and licking the genital area, improved earlier in Group CEF than in Group ENR ($P < 0.0001$ for all). Urine cultures giving values of ≤ 1000 CFU/ml were obtained on Days 17–21 after the first day of treatment in all dogs.

Table 2. Urine characteristics and distribution of clinical signs related to uncomplicated LUTIs in the two treatment groups. Dogs were administered enrofloxacin (5 mg/kg, *s.c.*, *s.i.d.*) for 14 days (Group ENR, *n* = 23) or a single dose of ceftriaxone (25 mg/kg, *i.v.*) (Group CEF, *n* = 20)

	Group ENR	Group CEF	Significance
Urine parameter (mean ± SD (CI))			
Specific gravity	1.024 ± 0.001 (1.010–1.030)	1.024 ± 0.001 (1.015–1.030)	$t = -0.012$ $P < 0.99$
pH	7.174 ± 0.212 (5.00–9.00)	7.175 ± 0.260 (5.00–9.00)	$t = -0.121$ $P < 0.63$
Clinical sign (*n* (%))			
Macroscopic haematuria	19 (82.6)	16 (80.0)	$\chi^2 = 0.83$ $P < 0.83$
Stanguria and dysuria	20 (86.96)	17 (85.0)	$\chi^2 = 0.85$ $P < 0.85$
Pollakuria	23 (100)	20 (100)	nd
Licking the genital area	13 (56.52)	12 (60.0)	$\chi^2 = 0.82$ $P < 0.82$

nd = not determined

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Table 3. Days (mean ± SD) needed to achieve clinical remission of signs in response to treatment with enrofloxacin (5 mg/kg, *s.c., s.i.d.*) for 14 days (Group ENR, n = 23) and a single dose of ceftriaxone (25 mg/kg, *i.v.*) (Group CEF, n = 20)

Clinical sign	Group ENR	Group CEF	*P*-value
Macroscopic haematuria	5.39 ± 0.60	0.80 ± 0.09	< 0.0001
Stranguria and dysuria	5.48 ± 0.59	3.20 ± 0.41	< 0.0001
Pollakuria	6.78 ± 0.30	3.45 ± 0.34	< 0.0001
Licking the genital area	3.65 ± 0.73	1.75 ± 0.39	< 0.0001

DISCUSSION

Uropathogens such as *E. coli* (47.4%), *Staphylococcus* spp. (11.6%), *Klebsiella* spp. (9.1%), *Enterococcus* spp. (8%) and *Proteus* spp. (9.3%) have been reported as the most common bacteria in dogs with urinary tract infections (Ling et al. 2001; Cohn 2003; Seguin et al. 2003). In agreement with the literature, *E. coli* was the most common bacterium (44.18%), followed by *Staphylococcus* spp. in the present study involving dogs with uncomplicated LUTI.

Enrofloxacin is an antimicrobial agent commonly used in veterinary medicine to treat urinary tract infections (Ettinger and Feldman 2010). It accumulates to particularly high concentrations within the urinary tract and, is efficacious against a spectrum of uropathogens (Polzin 1999). However, a dramatic increase in the development of bacterial resistance to canine uropathogens associated with the growing use of enrofloxacin has been reported (Cooke 2002; Cohn 2003). Ceftriaxone is a third generation, human-labelled cephalosporin with activity against a broad spectrum of Gram-positive and Gram-negative bacteria (Rodman et al. 1994). Its long half-life in humans means that it can be effective even after only a single administration. Utilisation of ceftriaxone may be advantageous due to its longer half-life and efficacy (Meyers et al. 1983; Moller 2002). The half-life and behaviour of ceftriaxone have exhibit varying tendencies in animals (Rebuelto et al. 2002). Dogs with uncomplicated LUTI are usually treated for 10–14 days (Grauer 2009; Weese 2011). However, only a few publications dealing with the efficacy of short term antibiotherapy in dogs with uncomplicated LUTI are available (Westropp et al. 2012; Clare 2014). The efficacy of short duration-high dose enrofloxacine treatment was tested in dogs with uncomplicated urinary tract disease (Westropp et al. 2012). In addition, short duration trimethoprim-sulfamethoxazole treatment was compared with long term cephalexine administration in dogs with uncomplicated bacterial cystitis (Clare 2014). It was reported that a single dose of cefovecin compared with multiple doses of cephalexin was an effective and safe treatment choice in dogs with uncomplicated LUTI (Passmore et al. 2007). Shorter duration or single dose antimicrobial regimens and their effects on symptom resolution were reported in human patients with uncomplicated LUTI (Iravani and Richard 1985; Arav-Boger et al. 1994; Bleidorn et al. 2010). Information on the efficacy of antibiotherapy (short vs long durations) in terms of achieving clinical remission is lacking in veterinary medicine. In the current study, the data on clinical remission parameters (Table 3) indicate that a single dose of ceftriaxone administration is superior to multiple doses of enrofloxacine for 14 days. Although 91.4% and 93.9% of uropathogens from dogs with uncomplicated urinary tract infections were susceptible to enrofloxacine and amoxicillin, respectively, the rate of clinical cure in response to the administration of these agents was lower than the values from susceptibility test (Westropp et al. 2012). In this study, isolated uropathogens were sensitive to both enrofloxacine and ceftriaxone with no significant differences identified between clinical and microbiological cures. The lack of differences in age, urine characteristics, breed, and frequency of sex as well as clinical signs (Tables 1 and 2) between groups, eliminates their confounding effects on outcome following the treatment protocols. However, administration of a single dose of ceftriaxone was more effective than administration of enrofloxacin (5 mg/kg, *s.c.*, *s.i.d.*) for 14 days, as shown by the fewer number of days required for alleviation of clinical signs (Table 3). The lack of of pre- and post-treatment minimum inhibitory concentration data for canine uropathogens isolated from the urinary tract is a major limitation of the current study. Further, our study would have benefited from a longer follow-up period in which to verify the complete microbiological eradication of LUTI.

In conclusion, ceftriaxone was well tolerated in dogs with uncomplicated LUTI without any side effects. Although a single dose of ceftriaxone can

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be considered as an alternative treatment in dogs with uncomplicated LUTI, its extensive use in clinical practise is limited by its status as a drug of last resort. Determination of minimum inhibitory concentration values for uropathogens in dogs will allow the calculation of most effective dosage.

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