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COMPARATIVE PHARMACOKINETICS OF ENROFLOXACIN AND MARBOFLOXACIN AFTER A SINGLE INTRAMUSCULAR ADMINISTRATION IN CAMEL

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ABSTRACT

The comparative serum pharmacokinetics of Enrofloxacin (E) and Marbofloxacin (M) were determined following an intramuscular dose of 5 mg/kg and 2.5 mg/kg body weight, respectively in camels. The data obtained was best fitted to 2-compartment open model. The maximum peak concentration of Enrofloxacin was 2.6 µg/ml and Marbofloxacin was 1.7 µg/ml obtained after 1.93 and 1.80 hours, respectively. The $t_{½}$ was 4.03 for Enrofloxacin and 7.1 hours for Marbofloxacin. The $t_{½}$, MRT and AUC were significantly greater for marbofloxacin than enrofloxacin.

Key words: Camel, Enrofloxacin, intramuscular, Marbofloxacin, pharmacokinetics

The major difference between the modern fluoroquinolones and nalidixic acid is the loss of the 8-nitrogen and the substitution of a fluorine at position 6 (Einsten *et al*, 2008). This results in increased activity against DNA gyrase and an extension of the antibacterial spectrum to Gram-positive organisms, including methicillin-resistant strains of *Staphylococcus aureus*. Activity against Streptococci, especially *enterococci*, is more variable. The fluoroquinolones have little activity against anaerobes, hence impact on the normal gastrointestinal microflora is minimal. Incorporation of a piperazine moiety, as in ciprofloxacin, increases activity against *Pseudomonas aeruginosa*. The older quinolones require dividing cells with intact protein synthesis but this is not necessary for the fluoroquinolones, which also may inhibit transfer RNA synthesis. The toxicity of these drugs is low (Vancutsem *et al*, 1990). A large number of fluoroquinolones are available for human use, including moxifloxacin, ciprofloxacin, enrofloxacin, enoxacin, levofloxacin, norfloxacin and ofloxacin and some of these have begun to be used in veterinary medicine. The synthetic potential of the quinolones is at an early stage, and a new class of antibacterial which combines a cephalosporin and a quinolone has been developed recently (RO 23-9424). This drug not only destroys the bacterial cell wall but also delivers the quinolone to its DNA target (Drlica and Zhao, 1997).

Although fluoroquinolones have been used successfully in the treatment of a wide range of conditions in both domestic and farm animals, no attention has been given to camels. The objective of this study was to compare the pharmacokinetic variables of 2 fluoroquinolones in the camel.

Materials and Methods

Ten clinically healthy 3-6 years old male and female camels with a body weight from 220-320 kg were used. Animals were allowed free access to hay and water.

Drug administration and sampling

Two independent studies each using 5 animals were performed. Enrofloxacin (5mg/kg, Baytril, Bayer, UK) and marbofloxacin (2.5mg/ml, Vetoquinol, UK) were injected intramuscularly (IM). Blood samples were collected at 0 (pre-treatment), 30 minutes, 1, 2, 4, 10 and 12 hours after administration of drugs. Blood samples were centrifuged at 2000g for 10 minutes and serum was separated and stored at -20°C until analysis.

Analytical procedures

Antibacterial activities in all samples were analysed by an agar diffusion assay (Klassn and Edberg, 1996) carried out on bioassay dishes (230-

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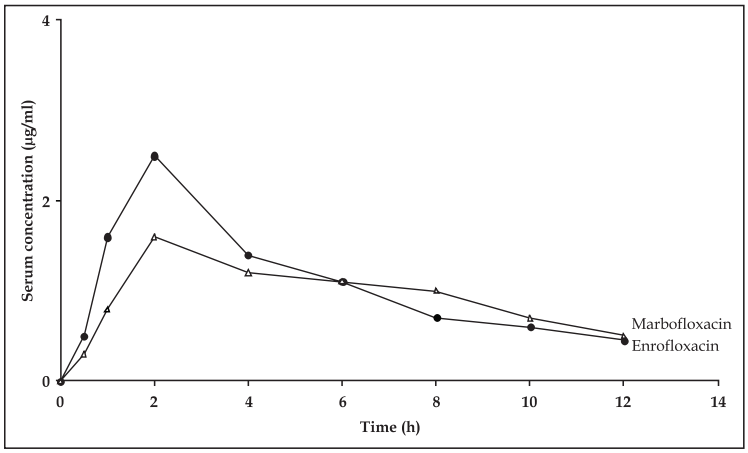

Fig 1. Mean semi-log plasma concentrations of enrofloxacin (5 mg/kg) and marbofloxacin (2.5 mg/kg) after single intramuscular administration to healthy camel (n=5 each).

230 mm, Nunc, Wiesbaden, Germany) containing balanced sensitivity test medium (BRL-Difco, Augsburg, Germany). A test organism *Klebsiella pneumoniae* ATCC 10031 was used. Pure substances (Bayer, Leverkusen, Germany) diluted in pooled blank cameline serum were used as reference standard. Plates were incubated at 37°C for 17-20 h. Inhibition zones were read with digital calipers.

Pharmacokinetic analysis

Compartmental pharmacokinetic analysis was performed with the serum concentration-time profile of individual animals using KINCALC software (Bayer, Leverkusen, Germany). The C_{max} and time to C_{max} (t_{max}) was determind from observed values. The $t_{1/2}$ was calculated by using the equation $t_{1/2}$ = In $2/l_z$ With l_z (terminal elimination rate constant) being determined by linear regression analysis of the concentration-time curve after logarithmic transformation. The AUC and area under the first moment curve (AUMC) were determined by applying the mixed logarithmic-Linear trapezoidal rule. The mean residence time (MRT) was determined from the equation MRT= AUMC\AUC.

Statistical analysis

Data were expressed as mean ± SD. Differences in pharmacokinetic parameters between the fluoroquinolones were compared using student's t-test and considered significant at $P < 0.05$.

Results

The mean serum concentration of enrofloxacin and marbofloxacin after single intramuscularly (IM) administration are given in Fig 1. The data was best fitted to 2-compartment open model. The pharmacokinetic parameters are given in Table 1. The maximum peak concentration of enrofloxacin was 2.6 µg/ml and marbofloxacin was 1.7 µg/ml obtained at 1.93 and 1.80 hours after IM injection, respectively. The half-lives were 4.03 and 7.1 hours for enrofloxacin and marbofloxacin, respectively. The $t_{1/2}$, MRT and AUC were significantly greater for marbofloxacin than enrofloxacin.

Discussion

The course describing the pharmacokinetic behaviour of enrofloxacin and marbofloxacin in camels look similar to other species; the drugs follow a 2-compartment open model (Boothe, 1994; Brimingham *et al*, 2000; Papich *et al*, 2002; Heinen, 2002). Both fluoroquinolones were rapidly absorbed and peak concentration were achieved within 1-3 hours. Significant differences between enrofloxacin and marbofloxacin were also reported elsewhere (Frazier *et al*, 2000). The results presented show that doses of 5 mg/kg of enrofloxacin and 2.5 mg/kg of marbofloxacin have produced sufficient serum concentration for C_{max} exceeding the minimum inhibitory concentration of 0.03-0.125 µg/ml for *E. coli* and 0.06-0.12 µg/ml for *Klabsiella pneumoniae* (Walker *et al*, 1992) for at least 24 hours suggesting dosing regimen once a day in the camel.

Enrofloxacin had a shorter elimination half-life than marbofloxacin. However, both drugs have a concentration-dependent activity and high pentration of tissue and cells (McKellar, 1996) as well as pronounced post antibiotic effect (Wetzstein and Jong, 1996). The $t_{1/2}$ values of enrofloxacin was shorter than the one reported for the mare (Papich *et al*, 2002), but similar to that reported for the dog (Heinen, 2002). The $t_{1/2}$ value for marbofloxacin was shorter than the one reported for the dogs. Because of longer elimination half-life, marbofloxacin has a significantly greater AUC than enrofloxacin (Heinen, 2002).

It is estimated that microbiologic assay overestimates the true enrofloxacin concentration as its metabolite ciprofloxacin may contribute to the antibacterial effect (Cester *et al*, 1996; Giguere *et al*, 1996); therefore, it is likely that the microbiologic assay measures the total activity which could be more useful for pharmacodynamic evaluation (McKellar, 1999). Furthermore, in inflammed tissues the phagocytic cells carry the fluoroquinolones to the site of infection (Carlier *et al*, 1990; Hawkins *et*

Table 1. Pharmacokinetic parameters for enrofloxacin (5 mg/kg) and marbofloxacin (2.5 mg/kg) after single intramuscular administration to camel (n=5 each).

Kinetic parameters	Enrofloxacin	Marbofloxacin
C_{max} (mg/ml)	2.6	1.7*
t_{max} (min)	1.93	1.8
$t_{½}$ (min)	4.03	7.1*
MRT (h)	6.80	11.6*
AUC (mg/ml/min)	9.1	12.6*

C_{max} = maximal plasma concentration; t_{max} = time to achieve maximal plasma concentration; $t_{½}$ = half-life; MRT = mean residence time and AUC = area under the curve.

* indicates significant difference ($P < 0.05$).

al, 1998) thereby significantly increasing tissue drug concentration (DeManuelle *et al*, 1998; McKellar *et al*, 1999) and eventually increasing the antibacterial activity. Although enrofloxacin and marbofloxacin are not registered anywhere for use in camel, and the manufacturing company give no clinical doses for the camel, its off-label use may be of value in treatment of gram-negative infection. This, however, should be confirmed by clinical studies.

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