

**KINETICS OF ENROFLOXACIN IN GOAT FOLLOWING INTRAVENOUS
AND INTRAMUSCULAR ADMINISTRATION**

Mohammed H. Al-Nazawi

Department of physiology, biochemistry and pharmacology,

College of veterinary medicine and animal resources,

King Faisal University, P. O. Box 3498, Al-Ahsa 31982,

Saudi Arabia.

malnazawi @ hotmail.com

ABSTRACT

Pharmacokinetics of enrofloxacin given intravenously (IV) and intramuscularly (IM) at a dose of 5 mg/kg to two groups of ardi goats were determined. The disposition of enrofloxacin was described by two-compartment open model with elimination half-life of 4.7 and 4.4 hours after IV and IM administration. Therapeutic serum concentration of the drug was achieved and maintained for 9 and 12 hours after administration by IV and IM, respectively. Volume of distribution was high after administration by either route but bioavailability was more after IM administration than by IV administration.

KEY WORDS: Pharmacokinetic, enrofloxacin, goat.

Introduction

Fluoroquinolones (FQs) have been shown to be effective in the treatment of a wide variety of bacterial infections in both humans and animals (Moellering 1996; Hooper, 1998). Fluoroquinolones have a broad bactericidal spectrum that includes Gram-negative and Gram-positive bacteria, chlamydiae and mycoplasma (Watts *et al.*, 1997; Wolfson and Hopper, 1989). Worldwide, the quinolones are used in veterinary medicine to treat a variety of bacterial infections (Brown, 1996; Walker, 2000). Enrofloxacin, difloxacin, marbofloxacin and orbifloxacin are member of the FQs, a class of synthetic antibacterial acting on bacterial DNA topoisomerases II and IV (gyrase) (Hooper and Wolfson, 1993; Drlica and Zhao, 1997). Enrofloxacin is rapidly absorbed from the site of administration and well distributed into tissues. It achieves extra- and intracellular inhibitory concentration (Scheer, 1987; Walker *et al.*, 1992; Kung *et al.*, 1993) facilitated by its amphoteric character and relatively low protein-binding (Brown, 1996; Boothe *et al.*, 1999). Enrofloxacin is a useful antimicrobial agent for veterinary application, it has a wide spectrum of antibacterial activity against organisms that are resistant to many other antibacterial substances. Such as β -lactam antibiotics, aminoglycosides, cephalosporins, tetracyclines, sulphonamides and macrolides (Scheer 1987; Spoo and Riviere, 1995). It is the most widely investigated FQ in dogs, rats, rabbits, monkeys, calves, pigs and human (Siefert *et al.*, 1986; Barrier *et al.*, 1987; Nouws *et al.*, 1988; Walker *et al.*, 1990; Andriole, 1993). Published pharmacokinetic data of FQs in goat are scarce and difficult to compare because different breeds of goat, administration procedure or analytical methods are used. Thus, the aim of the present study was to elucidate some of pharmacokinetic parameters of

enrofloxacin in healthy goats following intravenous (IV) or intramuscular (IM) administration of a single dose.

MATERIALS AND METHODS

Animals:

Ten healthy female adult goats of ardi breed aged 3-4 years and weighed between 45-55 kg were used in this study. They were housed in separate pens under natural day length and temperature. Goats were allowed to rest for certain time to make sure none of them had received any medication for at least 8 weeks prior enrofloxacin administration. Water, hay and concentrate supplements were provided *ad libitum*. Animals were then divided randomly into two groups; IV-group and IM-group.

Drug administration and sampling:

Enrofloxacin sodium (Hipra, 17170 Amer, Girona, Spain) was dissolved in 5 ml of sterile 0.9% sodium chloride solution. Each goat of the two groups was received a single dose of 5 mg/kg body weight either IV or IM. Blood samples (5 ml) for determination of serum enrofloxacin concentration were collected from the jugular vein into tubes prior to (time 0) and at predetermined times between 5 minutes and 48 hours after drug administration. Samples were allowed to stand protected from light for 20 min, then centrifuged at $1400 \times g$ for 5 min. Serum was separated and stored at -20°C until analysis. Concentration of the drug in the serum was determined spectrophotometrically by modified method of Jha *et al.*, (1996). The absorbance maxima of enrofloxacin were recorded at 278 nm. Drug standard and control of serum were always run in a similar manner adopted for unknown samples.

Pharmacokinetics analysis:

The relevant pharmacokinetic parameters were calculated according to conventional equations associated with compartmental analysis (Gibaldi and Perrier, 1982). The area under the concentration versus time curve (AUC) was calculated using the trapezoidal rule to the last measured concentration and also with extrapolation to infinity. The mean residence time (MRT) was calculated according to the equation ($MRT = AUMC/AUC$), where AUMC is the area under the curve of a plot of the product of time and the plasma drug concentration versus time. The mean absorption time (MAT) was calculated as $MAT = MRT$ of intravenous, MRT of intramuscular routes. The intramuscular bioavailability (F) was calculated by the method of corresponding areas as $F = AUC_{i.m.} / AUC_{i.v.}$.

Statistical analysis:

Differences in pharmacokinetic data between IV and IM routes were calculated for statistical significance by Mann-Whitney test. *P-value* < 0.05 was considered significant.

RESULTS

Enrofloxacin concentration versus time curves was generated from data obtained after IV administration (Fig. 1). The values of pharmacokinetic parameters, which described the absorption and disposition kinetics of enrofloxacin in goats, are given in table 1. Mean elimination half-life was 4.7 hours (h), and mean residence time was 5.4 h. Whereas the area under the concentration versus time curve (AUC) equal 2.23 $\mu\text{g/ml}$. Mean volume of the central compartment (1.5 l/kg) and volume of distribution at steady state (3.1 l/kg) were high, which are indicative of good tissue distribution. The ratio of the rate of distribution from the central to the peripheral compartment and vice versus indicating that drug transportation rates was approximately equal.

Enrofloxacin concentration versus time curves was generated from data obtained after IM administration (Fig. 2). The values of pharmacokinetic parameters, which described the absorption and disposition kinetics of enrofloxacin in goats, are given in table 2. The absorption was rapid, mean absorption half-life was 0.15 h. The mean C_{max} of 0.33 $\mu\text{g/ml}$ was achieved in 0.74 h. Volume of distribution and AUC were similar to values obtained after IV administration.

DISCUSSION

Pharmacokinetics of enrofloxacin in goats have not been documented, so it's difficult to compare the results in present study with results of previous studies. However, there are studies of enrofloxacin pharmacokinetics in calves (Kaartinen *et al.*, 1995), dogs (Heinen, 2002; Ehinger *et al.*, 2002) and mares (Papich *et al.*, 2002). Peak of enrofloxacin concentration in goat serum was demonstrated. With regards to the elimination half-life, the results have shown that effective level of enrofloxacin was maintained in goat for 4.7 and 4.4 h after IV and IM dosing, respectively. In other animals a considerable amount of work has demonstrated the acceptable serum concentrations of enrofloxacin. The elimination half-life in pigs, calves, dog and horse and were, 4.99, 3.88, 4.07 and 6.7 hours, respectively (Anadon *et al.*, 1995; Saini *et al.*, 2001; Heinen, 2002; Papich *et al.*, 2002). The outcome of this study was that enrofloxacin elimination half-life values were lower than those of pigs, dogs and horse but higher than calves. Mean V_d in goat was found at three times more after both IV than IM administration; equally high values have been obtained for other ruminant species (Kaartinen *et al.*, 1995; Brown, 1996; Mengozzi, 1996; Walker, 2000; Rao *et al.*, 2002). In addition volume of the central compartment was high after IV administration. This indicates that the drug likely moves rapidly from the extracellular fluid into cells. Area under the concentration versus time curves following IV and IM administration was identical. Moreover, the brief absorption half-life indicates rapid absorption from the IM injection site in goats. Although, both routes produced therapeutic level, enrofloxacin given intramuscularly was absorbed and eliminated slower than that administered intravenously. In conclusion, IM administration of enrofloxacin was superior in maintaining therapeutic concentration for a longer period of time.

ACKNOWLEDGEMENTS

The author thanks the Deanship of Scientific Research, King Faisal University for financial support.

Table- 1: Pharmacokinetic parameters of enrofloxacin given at a single IV dose of 5 mg/kg body weight to healthy goats (n. = 5).

Kinetic parameters	Mean \pm SD
C_{\max} ($\mu\text{g/ml}$)	0.88 ± 0.21
A ($\mu\text{g/ml}$)	0.61 ± 0.10
α (h^{-1})	1.47 ± 0.25
$t_{1/2}$ (α) (h)	0.56 ± 0.02
B ($\mu\text{g/ml}$)	0.27 ± 0.04
β (h^{-1})	0.16 ± 0.06
$t_{1/2}$ (β_1) (h)	4.7 ± 0.45
K_{12} (h^{-1})	0.60 ± 0.15
K_{21} (h^{-1})	0.63 ± 0.13
K_{12}/K_{21}	1.0 ± 0.05
MRT (h)	5.33 ± 0.44
AUC ($\mu\text{g/ml/h}$)	2.23 ± 16
Cl_B (L/kg/min)	0.57 ± 0.03
V_d (area) (L/kg)	3.80 ± 0.36

C_{\max} = maximum drug concentration; A = zero-time intercept of distribution phase; B = zero-time intercept of elimination phase; α = distribution constant; $t_{1/2}$ (α) = half-life of distribution phase; β = elimination constant; $t_{1/2}$ (β_1) = half-life of elimination phase; K_{12} = rate constant from central to peripheral compartment; K_{21} = rate constant from peripheral to central compartment; K_{12}/K_{21} = ratio of K_{12} to K_{21} ; MRT = mean resident time; AUC = area under the concentration-time curve; V_d (area) = volume of drug distribution; Cl_B = total body clearance of the drug.

Table- 2: Pharmacokinetic parameters of enrofloxacin given at a single IM dose of 5 mg/kg body weights, to healthy goats. (n. = 5).

Kinetic parameters	Mean \pm SD
C_{\max} ($\mu\text{g/ml}$)	0.33 ± 0.02
AUC ($\mu\text{g/ml/h}$)	2.29 ± 0.12
K_{abs} (h^{-1})	5.90 ± 1.02
$T_{1/2\text{abs}}$ (h^{-1})	0.15 ± 0.02
K_{el} (h^{-1})	0.16 ± 0.02
$T_{1/2\text{el}}$ (h)	4.41 ± 0.12
F (%)	110 ± 9.8

C_{\max} = peak concentration; $t_{1/2}(\alpha)$ = half-life of distribution phase; AUC = area under the concentration-time curve K_{abs} = absorption rate constant; $T_{1/2\text{abs}}$ = absorption half-life; K_{el} = tissue fluid elimination rate constant; $T_{1/2\text{el}}$ = tissue fluid elimination half-life; F = bioavailability.

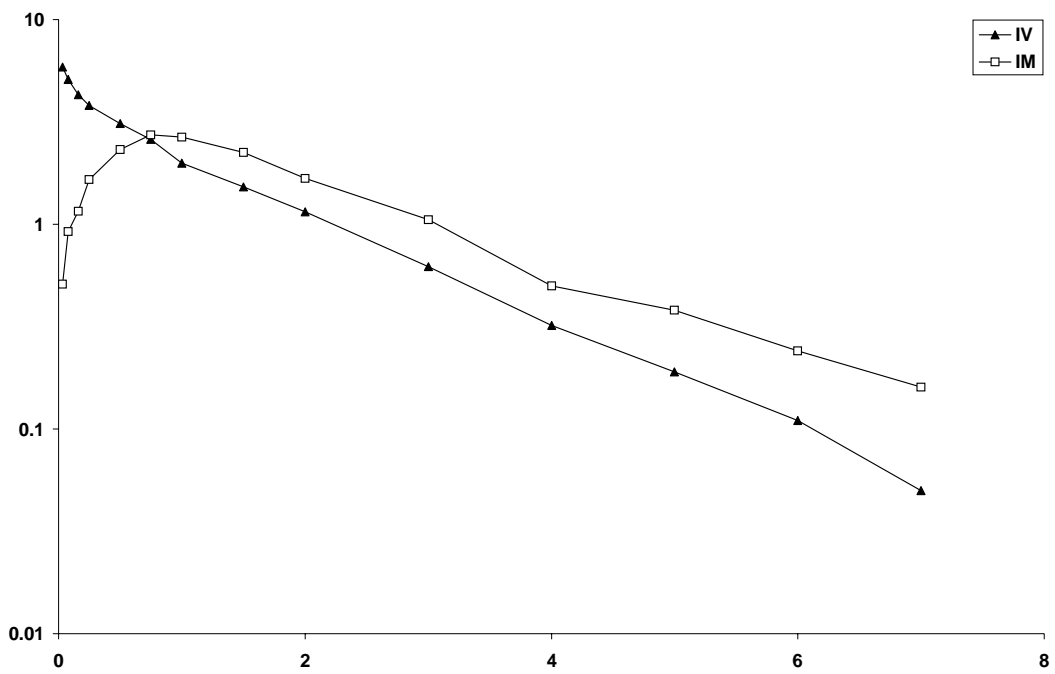


Fig 1: Mean serum concentrations of enrofloxacin following a single IV and IM dose of 5 mg/kg body weights to healthy goats. (n. = 5 each).

References

Andriol V. T. (1993). The future of the quinolones. *Drugs*, 45 (Suppl. 3): 1-7.

Barriere S. I., Kaatz G. W., Schaberg D. R. and Fekety R. (1987). Altered pharmacokinetic disposition of ciprofloxacin and vancomycin after single and multiple doses in rabbits. *Antimicrob. Agents Chemother.*, **31**: 1075-1078.

Boothe D. M., Boeckh A., Wilkie S. and Boothe H. W. (1999). Antimicrobial movement into tissues: the impact of antimicrobial accumulation by phagocytes. *Compend. Contin. Educ. Pract. Vet.*, **21**(Suppl., 12M): 26-31.

Brown S. A. (1996). Fluoroquinolones in animal health. *J. Vet. Pharmacol. Therap.* **19**: 1-14.

Drlica K. and Zhao X. (1997). DNA gyrase, topoisomeras IV and the 4-quinolones. *Microbiol. Molecul. Biol. Rev.*, **61**: 377-392.

Ehinger A. M., Meyer-Lindenberg A., Vick, M, Nolte I. and Kietzmann M. (2002). Concentration of enrofloxacin and its metabolite ciprofloxacin in canine matrices of the locomoter system. *J. Vet. Med.*, **49**: 99-104.

Gibaldi M and Pirrier D. (1982). *Pharmacokinetics*. New York: MarcellDekker.

Heinen E (2002). Comparative serum pharmacokinetics of the flouroquinolones enrofloxacin, difloxacin, marbofloxacin, and orbifloxacin in dogs after single oral administration. *J. Vet. Pharmacol. Therap.* **25**: 1-5.

Hooper D. C. (1998). Clinical applications of quinolones. *Biochimica et Biophysica Acta* **1400**: 45-61.

Hooper D. C. and Wolfson J. S. (1993). Mechanisms of quinolone action and bacterial killing. In: Quinolone Antimicrobial Agents. 2nd. edn., Eds., Hooper D. C. and Wolfson J. S. American Society for Microbiology, Washington, pp.53-76.

Jha K. Roy B. K. and Singh R. C. P. (1996). The effect of induced fever on the biokinetics of norfloxacin and its interaction with probenecid in goats. *Vet. Rese. Commun.*, **20**:473-479.

Kaartinen L., Salonen M., Alli L. and Pyorala S. (1995). Pharmacokinetics of enrofloxacin after single intravenous, intramuscular and subcutaneous injections in lactating cows. *J. Vet. Pharmacol. Therap.* **9**: 254-263.

Kung K., Rioud J. L. and Wanner M. (1993). Pharmacokinetics of enrofloxacin and its metabolites ciprofloxacin after intravenous and oral administration of enrofloxacin in dogs. *J. Vet. Pharmacol. Therap.*, **16**: 462-468.

Mengozi G., Intorre L., Bertini S. and Soldani G. (1996). Pharmacokinetics of enrofloxacin and its metabolite, ciprofloxacin after intravenous and intramuscular administration in sheep. *Am. J. Vet. Rese.*, **57**: 1040-1043.

Moellering R. C. (1996). The place of quinolones in every clinical practice. *Chemotherapy* **24**: 54-61.

Nouws J. F. M., Mevius D. J., Vree, T. B., Baars A. M. and Laurensen J. (1988). Pharmacokinetics, renal clearance and metabolism of ciprofloxacin following intravenous and oral administration to calves and pigs. *Vet. Quarterly*, **10**: 156-163.

Papich M. G., Van-Camp S. D., Cole J. A. and Whitacre M. D. (2002). Pharmacokinetics and endometrial issue concentrations of enrofloxacin and the metabolite ciprofloxacin after i.v. administration of enrofloxacin to mares. *J. Vet. Pharmacol. Therap.*, **25**: 343-350.

Rao G. S., Ramesh S., Ahmad A. H., Tripathi H. C., Sharma L. D. and Malik J. K. (2002). Pharmacokinetics of enrofloxacin and its metabolite, ciprofloxacin in goat given enrofloxacin alone and in combination with probenecid. *Vet. J.*, **163**: 85-93.

Scheer M. (1987). Concentration of active ingredient in the serum and in tissues after oral and parenteral administration of batyryl. *Vet. Med. Rev.*, **2**: 104-118.

Siefert H. M., Maruhn D., Maul W., Forster D. and Ritter W. (1986). Absorption, concentrations in plasma, metabolism and excretion after a single administration of [¹⁴C] ciprofloxacin in albino rats and rhesus monkeys. *Drug Res.*, **36**: 1496-1502.

Spoo J. W. And Riviere J. E. (1995). Chloramphenicol, macrolides, lincosamides, fluoroquinolones and miscellaneous antibiotics. In: *Veterinary pharmacology and therapeutics*, 7th edn. Ed. Adams, H. R. Ames, Iowa State University Press, pp. 820-854.

Walker R. D. (2000). The use of fluoroquinolones for companion animal antimicrobial therapy. *Australian Vet. J.*, **78**: 84-89.

Walker R. D., Stein G. E., Hauptman J. G. and MacDonald K. H. (1992). Pharmacokinetic evaluation of enrofloxacin administered orally to healthy dog. *Am. J. Vet. Res.*, **53**: 2315-2319.

Walker R. D., Stein G. E., Hauptman J. G., MacDonald K. H., Budsberg S. C. and Rosser E. J. (1990). Serum and tissue cage fluid concentration of enrofloxacin after orally administration of the drug to healthy dogs. *Am. J. Vet. Res.*, **51**: 896-900.

Watts J. L., Salmon S. A., Sanchez M. S. and Yancey R. J. (1997). In vitro activity of premafloxacin, a new extended-spectrum fluoroquinolone against pathogens of veterinary importance. *Antimicrobial Agents and Chemotherapy*, **41**: 1190-1192.

Wolfson J. S. and Hooper D. C. (1989). Fluoroquinolone antimicrobial agents. *Clinical Microbiology Review*, **2**: 378-424.