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Dr. VK Gond
Assistant Professor, Animal Production Research Institute, D.R.P.C.A.U., Pusa, Samastipur, Bihar, India

Dr. Nirbhay Kumar
Assistant Professor & Head, Department of Veterinary Pharmacology & Toxicology, Bihar Veterinary College, Patna, Bihar, India

Dr. Dhiraj Kumar
Ex-PG Scholar, Department of Veterinary Pharmacology & Toxicology, Bihar Veterinary College, Patna, Bihar, India

Dr. C Jayachandran
Ex-Professor and Head, Department of Veterinary Pharmacology & Toxicology, Bihar Veterinary College, Patna, Bihar, India

Dr. RK Sharma
Professor and Head, Department of Veterinary Pharmacology & Toxicology, College of Veterinary Science & Animal Husbandry, N.D.V.S.U., Jabalpur, Madhya Pradesh, India

Dr. K Shrman
Associate Professor, Department of Veterinary Pharmacology & Toxicology, College of Veterinary Science & Animal Husbandry, N.D.V.S.U., Jabalpur, Madhya Pradesh, India

Dr. P Mishra
Ph.D. Scholar, Department of Veterinary Pharmacology & Toxicology, College of Veterinary Science & Animal Husbandry, N.D.V.S.U., Jabalpur, Madhya Pradesh, India

Corresponding Author:
Dr. Nirbhay Kumar
Assistant Professor & Head, Department of Veterinary Pharmacology & Toxicology, Bihar Veterinary College, Patna, Bihar, India

Disposition kinetics of enrofloxacin and its metabolite ciprofloxacin after intravenous, intramuscular and oral administration of enrofloxacin in goats

Dr. VK Gond, Dr. Nirbhay Kumar, Dr. Dhiraj Kumar, Dr. C Jayachandran, Dr. RK Sharma, Dr. K Shrman and Dr. P Mishra

Abstract
The present study was conducted to reveal the disposition kinetics of enrofloxacin (ENR) and its active metabolite ciprofloxacin (CPR) in healthy goats following single intravenous (IV), intramuscular (IM) and oral administration at the dose rate of 5 mg.kg^{-1} body weight. Blood samples were collected at time intervals of 0.042, 0.083, 0.125, 0.333, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours post drug administration. On the basis of a semi-log plot of the plasma drug concentration versus time curve, the pharmacokinetic parameters of ENR were estimated by IV, IM and oral routes. ENR metabolized to CPR, also exerts potential antimicrobial activity at very low concentration. The two-compartment open model for ENR (IV route), the one-compartment open model (IM and oral routes) and non-compartmental analysis for CPR provided best results for the experimental data. The therapeutic concentration of ENR (≥ 0.125 µg.ml^{-1}) was maintained till 24 hours after a single intravenous and 12 hours after intramuscular and oral dosage, respectively. The mean elimination ($t_{½}$ β) half-lives after IV, IM and oral administration were 3.93±0.46, 3.10±0.34 and 2.94±0.16 h, respectively, while the mean residential time (MRT) was 4.58±0.63, 5.54±1.13 and 4.62±0.18 h. Following IM and oral dosing, the mean bioavailability (F) was 84.46±10.12 and 63.68±1.59, respectively. In comparison to IV, IM and oral routes of drug administration, the elimination rate constant and half-life ($t_{½}$ β), total body clearance (Cl_B), were found to be significant. The absorption rate constant (α), Vd_{area}, and MRT were found to be non-significant. It can be concluded that enrofloxacin may therefore be successful in treating susceptible bacterial infections in goats whether administered intravenously, intramuscularly or orally given at a dose level of 5 mg.kg^{-1} body weight twice daily.

Keywords: Enrofloxacin, ciprofloxacin, antibacterial, pharmacokinetics, bioavailability, HPLC, goats

Introduction
Antimicrobial therapy constitutes a major component of modern medical and veterinary practices. A class of antibiotics known as fluoroquinolones has revolutionised clinical treatment in both humans and animals. There have been many different molecules created. Norfloxacin, enrofloxacin, ciprofloxacin, pefloxacin, ofloxacin, sparfloxacin, and gatifloxacin are the fluoroquinolones that are used the most frequently. Enrofloxacin is a fluoroquinolone of the second generation that was created in 1983 by the Bayer Research Laboratory in Germany specifically for veterinary usage. It has broad-spectrum, bactericidal antimicrobial activity against both gram-positive bacteria and Mycoplasma, as well as gram-negative bacteria such *Escherichia coli, Salmonella, Klebsiella, Proteus, Haemophilus, Pasteurella, Campylobacter and Pseudomonas* spp [1-2].
Enrofloxacin has excellent bio-availability with superior pharmacokinetic profiles (better absorption and distribution in body fluids and tissues). The Minimum Inhibitory Concentration (MIC) of enrofloxacin in blood ranges from 0.01–2 µg.ml^{-1}. It is a potent inhibitor of the DNA-gyraze enzyme. Enrofloxacin can be used to treat a variety of microorganisms that are resistant to β–lactam antibiotics, aminoglycosides, tetracycline, macrolides and folic acid antagonist. Development of cross-resistance with other antimicrobials is rare. In order to treat local as well as systemic infections of the uterus, mammary gland, soft tissues, bone etc., it was especially developed for use in veterinary medicine.
The fact that enrofloxacin is metabolised (de-ethylated) into ciprofloxacin, which also exhibits potential antibacterial activity at very low concentrations, is an added benefit [3-4]. Both ciprofloxacin and enrofloxacin are bactericidal drugs that are anticipated to work in concert to kill gram-negative and gram-positive bacteria as well as Mycoplasma [2].

Both enrofloxacin and ciprofloxacin are bactericidal drugs that are expected to act synergistically to kill gram-negative and gram-positive bacteria and Mycoplasma [2]. Enrofloxacin is rapidly absorbed and evenly distributed throughout the body after being administered intramuscularly and orally to animals [5].

The bioavailability of an antibiotic is crucial in clinical practice. Both the rate and the amount of absorption are factors in bio-availability. Any medicine supplied intravenously is completely bioavailable, but when provided extravascularly (intramuscularly, subcutaneously, orally, for example), bioavailability varies greatly due to variations in absorption rate and volume. Systemic medications given parenterally or orally need to enter the general circulation in order to be disseminated throughout the body and have a therapeutic effect.

With a single dose of medication, the rate of absorption is therapeutically significant, particularly with drugs with a narrow therapeutic index where relatively small changes in concentration can result in noticeable changes in pharmacodynamic response, particularly toxic effects, as in the case of aminoglycosides. With numerous medications, it was also shown that bioavailability varied from species to species. It is also known that a drug's bioavailability varies depending on the pharmaceutical company that made it.

Enrofloxacin pharmacokinetic investigations have been carried out on cow calves [6], cows [7], horses [8], sheep [9-10], buffalo calves [11], goats [12] and chicken [13]. Kinetics and bioavailability of enrofloxacin was studied in pigs [14] and mares [15]. However, it appears that limited research on goat have been conducted. Despite enrofloxacin's enormous potential for clinical usage, we sought to assess the drug's disposition kinetics and that of its active metabolite, ciprofloxacin, in goats following a single intravenous, intramuscular and oral dose of the drug.

Material and Methods

Animals

In the present investigation, five clinically healthy female goats of non-descript breed between 18-24 months of age and 17-20 kg body weight were used. The goats were housed in the animal shed in the Department of Veterinary Pharmacology and Toxicology, Bihar Veterinary College, Patna. The goats were maintained on dry fodder concentrate and green grasses apart from routine grazing of about 4 to 5 hours.

Experimental design

A single-dose, randomised, crossover study with a minimum 15-day washout interval was conducted. Each animal received 5 $mg.kg^{-1}$ of enrofloxacin (Floxidin 10%, Intervet, India) intravenously (IV), intramuscularly (IM) and orally. Enrofloxacin was given as a bolus for IV administration using a catheter inserted into the left jugular vein. Enrofloxacin was injected into the semitendinosus muscle for IM delivery. A catheter was inserted into the right jugular vein to collect blood samples (2 ml), which were then put into tubes containing the anticoagulant heparin at the following times: 0 (pre-treatment), 0.042, 0.083, 0.125, 0.333, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h after the dose. Blood samples (10 ml) were taken from each animal prior to the administration of enrofloxacin for validation experiments. For the purpose of separating the plasma, samples were centrifuged at 3000 rpm for 15 minutes. After that, plasma samples were stored at -20 °C in a refrigerator till analysis.

HPLC assay of ENR

High performance liquid chromatography (HPLC) was used to determine the plasma enrofloxacin concentrations, somewhat modifying the methods previously published [14, 16]. The temperature of frozen plasma samples (-20 °C) was raised to ambient. Plasma samples (400 µl) were put into micro-centrifuge tubes. The tubes were combined on a vortex for 60 seconds after adding 600 µl of acetonitrile to prevent protein denaturation and then centrifuged at 3000 rpm for 15 minutes. After transferring the supernatants (300 µl) into fresh tubes, adding 600 µl of triple-distilled water and vortexing the tubes for 10 s. The injector's loop received an aliquot of this mixture (up to 400 µl) and the integrator recorded (printed out) the retention time and area.

The HPLC equipment used comprised of a HPLC pump (Model 515-Waters), a dual wavelength absorbance detector (Model 2487-Waters), a rheodyne manual injector with a 200 µg loop size and a data module (Model 746 – Waters). Chromatographic separations were performed using column 3.9 x 300 mm (µ Bondapak^{TM} C_{18}-Waters). The flow rate was 0.6 $ml.min^{-1}$, the effluent wavelength was monitored at 278 nm. Loop size was 200 µl, injection volume was 400 µl, the chart speed was 0.25 $mm.min^{-1}$ and the detector sensitivity was 2.000 A.U.F.S (Absorbance under full scale) were adopted for HPLC analysis for enrofloxacin and its active metabolite ciprofloxacin. The mobile phase comprised of acetonitrile: methanol: water (17: 3: 80 v/v/v) containing 0.4% phosphoric acid (85% v/v) and 0.4% triethylamine (v/v). The pH of mobile phase was adjusted to 3.0.

Pharmacokinetic analysis

From a semilog plot of the plasma drug concentration versus time curve, the pharmacokinetic characteristics of enrofloxacin after a single IV, IM, and oral dose were calculated. The experimental data were analysed using a two-compartment open model for enrofloxacin (IV route), a one-compartment open model (IM and oral routes) and a non-compartmental analysis for ciprofloxacin [17-18]. The following equation can be used to calculate the drug's plasma concentration at any given time:

$C_p = A_e^{-\alpha t} - B_e^{-\beta t}$……..(One compartment model)

$C_p = A_e^{-\alpha t} + B_e^{-\beta t}$……..(Two compartment model)

Where e is the base of natural logarithm and C_p is the drug concentration in plasma at time ‘t’.

Statistical analysis

Statistical analysis was done by using single factor Anova [19].

Result and Discussion

After a single IV, IM and oral administration of enrofloxacin (Figure 1), drug maintained its therapeutic concentration (≥ 0.125 $\mu g.ml^{-1}$) in plasma for a period of more than 12 h in goats. In contrast, when enrofloxacin was given to buffalo calves [11] at a dose rate of 4 $mg.kg^{-1}$ body weight by IV route, it was observed that the drug was detectable only up to 12 h. In another study, enrofloxacin appeared in goats up to 24 hours after intravenous administration at an effective quantity [20].

Following IV, IM and oral administration of enrofloxacin, the active metabolite of enrofloxacin *i.e.* ciprofloxacin was detected up to 24 hours in plasma in goats (Figure 2). The

elimination half life ($t_{1/2}\beta$) was found to be 3.33±0.72, 3.46±0.35 and 3.38±0.44 in IV, IM and oral routes, respectively which differed non-significantly.

After a single IV injection, it was discovered that ciprofloxacin had a more or less comparable $t_{1/2}\beta$ of 4.71±0.67 h in goats [18]. In buffalo calves, a somewhat lower $t_{½}\beta$ of 2.40±0.33 h following IV treatment was reported [11]. AUC, AUMC and the percentage of enrofloxacin that was converted to ciprofloxacin (AUC_{cipro}/AUC_{enro}) were all shown to be significantly higher in the IM and oral routes than in the IV. The IV route was shown to have much greater levels of many other kinetic parameters (Vd_{SS} & Cl_B) than the IM and oral routes. The percentage conversions were roughly similar (36%) in goats after receiving enrofloxacin by IM route [21].

With mean values of 0.18±0.02, 0.23±0.02, 0.24±0.0 and 3.93±0.46, 3.10±0.34, 2.94±0.16 after IV, I.M. and oral treatment, respectively, the elimination rate constant (β) and elimination half life ($t_{1/2}\beta$) were reported to be significantly higher in IV administration. This is in agreement with ($t_{1/2}\beta$) following IV and IM administration of 4.02 hours and 4.00 hours in goat [20], 3.30 hours and 3.87 hours [10], and 3.73 hours and 3.65 hours in sheep [9]. Enrofloxacin's rapid absorption and somewhat slower drug elimination after intramuscular administration are reflected by its absorption half-life ($t_{1/2}Ka$) and elimination half-life ($t_{1/2}\beta$).

With mean values of 24.87±2.39, 19.04±1.84, 15.82±1.50 and 113.33±17.30, 105.19±22.02, 73.73±7.90 after IV, IM and oral administration, respectively, the AUC and AUMC were reported to be significantly higher in IV administration. The biological availability of the active moiety of a drug formulation (extent of absorption) can be determined by looking at the area under the drug concentration time curve (AUC). The AUC values in this study are higher or comparable to earlier findings in goats [20]. When enrofloxacin is administered to goats orally, intravenously, or both, several of the kinetic parameters, including as MRT, Vdarea and Tmax (h), do not differ significantly. Following the IV injection of enrofloxacin to goat, a more or less comparable Vd_{area} of 1.42 $L.kg^{-1}$ was reported [21].

In cow, an MRT of 7.98±1.17 h [22] or close to it was seen following IM treatment. T_{max} values of 1.68 h [23] and 2.0 h [24] following a single oral administration at a dose level of 10 $mg.kg^{-1}$ body weight are in agreement with the current findings. Comparing the oral route to the IM method, the bioavailability (F%) was significantly lower in the oral route (63.68±1.59) than in the IM route ($84.46^{\pm}10.12$). The bioavailability in this experiment is comparable to 59.60% [13], 64.0% [23] in chicken and 47.89% [25] in sheep when administered orally.

Dosage regimen

Table 3 represents the dosage regimens needed to maintain various therapeutic plasma levels of enrofloxacin at 0.125, 0.25, and 0.50 $\mu g.ml^{-1}$ for intravenous, intramuscular and oral routes in goats (n=5) at convenient dosing intervals (h) of 8 and 12 h. For the IV and IM routes, the predicted dosage regimens (D* and D_0) are shown to be non-significant. Although the doses (D* and D_0) for the oral route are significantly larger. Enrofloxacin is so anticipated to be equally efficacious in goats when administered intravenously, intramuscularly and orally.

Table 1: Kinetic parameters (Mean±S.E.M.) of enrofloxacin following single intravenous, intramuscular and oral administration in goats (n=5).

Kinetics Parameters	IV	IM	ORAL
α (h^{-1})	$2.49^{\pm}0.39$		
$t_{1/2}$ α (h)	0.33±0.08		
Ka (h^{-1})		2.45±0.35[a]	$2.05^{\pm}0.49$[b]
$t_{1/2}$ Ka(h)		0.31±0.04[a]	0.39±0.06[a]
β (h^{-1})	0.18±0.02[a]	0.23±0.02[b]	0.24±0.01[b]
$t_{1/2}$ β (h)	3.93±0.46[a]	3.10±0.34[b]	2.94±0.16[b]
AUC ($mg.L^{-1}.h$)	24.87±2.39[a]	$19.04^{\pm}1.84$[b]	$15.82^{\pm}1.50$[b]
AUMC ($mg.L^{-1}.h^2$)	113.33±17.30[a]	105.19±22.02[b]	73.73±7.90[c]
MRT (h)	4.58±0.63[a]	5.54±1.13[a]	4.62±0.18[a]
Vd_{area} ($L.kg^{-1}$)	1.22±0.14[a]	$1.21^{\pm}0.15$[a]	1.37±0.12[b]
Cl_B ($ml.kg^{-1}min^{-1}$)	$3.63^{\pm}0.36$[a]	$4.53^{\pm}0.43$[b]	5.41±0.43[c]
C_{max} ($\mu g.ml^{-1}$)		5.35±0.87[a]	4.24±0.78[b]
T_{max} (h)		1.60±0.09[a]	1.70±0.12[a]
F (%)		$84.46^{\pm}10.12$[a]	$63.68^{\pm}1.59$[b]

Different superscripts denote significant difference ($p<0.05$)

Table 2: Kinetic parameters (Mean±S.E.M.) of ciprofloxacin following intravenous, intramuscular and oral administration of enrofloxacin in goats (n=5).

Kinetics Parameters	IV	IM	ORAL
β (h^{-1})	0.24±0.04	0.20±0.02	0.21±0.03
$t_{1/2}$ β (h)	3.33±0.72	3.46±0.35	3.38±0.44
AUC ($mg.L^{-1}.h$)	1.62±0.34	8.82±1.18	7.17±1.75
AUMC ($mg.L^{-1}.h^2$)	6.49±0.69	44.35±7.51	35.00±9.78
Vd_{SS} ($L.kg^{-1}$)	26.53±15.86	3.05±0.53	4.41±0.79
Cl_B ($mg.kg^{-1}.min^{-1}$)	69.57±24.00	5.97±2.13	13.83±5.22
% conversion of enrofloxacin to ciprofloxacin $\left(\frac{AUC\ cipro}{AUC\ enro}\right)$	6.98±1.53	48.10±7.58	48.06±11.76

Table 3: Dosage regimen (Mean±S.E.M.) of enrofloxacin for intravenous, intramuscular and oral route in goat (n=5).

C_p^{∞} min (µg.ml^{-1})	γ (h)	Dose type (mg.kg^{-1})	Dose regimen (Mean±S.E.M.)		
			IV	IM	ORAL
0.125	8	D*	0.61±0.05	0.58±0.11	0.97±0.18
		D_0	0.46±0.05	0.46±0.10	0.85±0.19
	12	D*	1.29±0.18	1.37±0.39	3.13±1.02
		D_0	1.14±0.19	1.26±0.39	3.01±1.03
0.25	8	D*	1.23±0.11	1.16±0.21	1.93±0.37
		D_0	0.92±0.10	0.93±0.21	1.70±0.38
	12	D*	2.58±0.36	2.74±0.78	6.20±2.04
		D_0	2.28±0.38	2.52±0.78	6.03±2.06
0.50	8	D*	2.45±0.20	2.32±0.43	3.87±0.74
		D_0	1.85±0.21	1.86±0.42	3.41±0.76
	12	D*	5.16±0.73	5.49±1.57	12.50±4.07
		D_0	4.56±0.77	5.04±1.56	12.07±4.12

D*= Priming or Loading dose
D_0= Maintenance dose
γ = Dosage interval
C_p^{∞} min = Minimum therapeutic concentration in plasma (MIC).

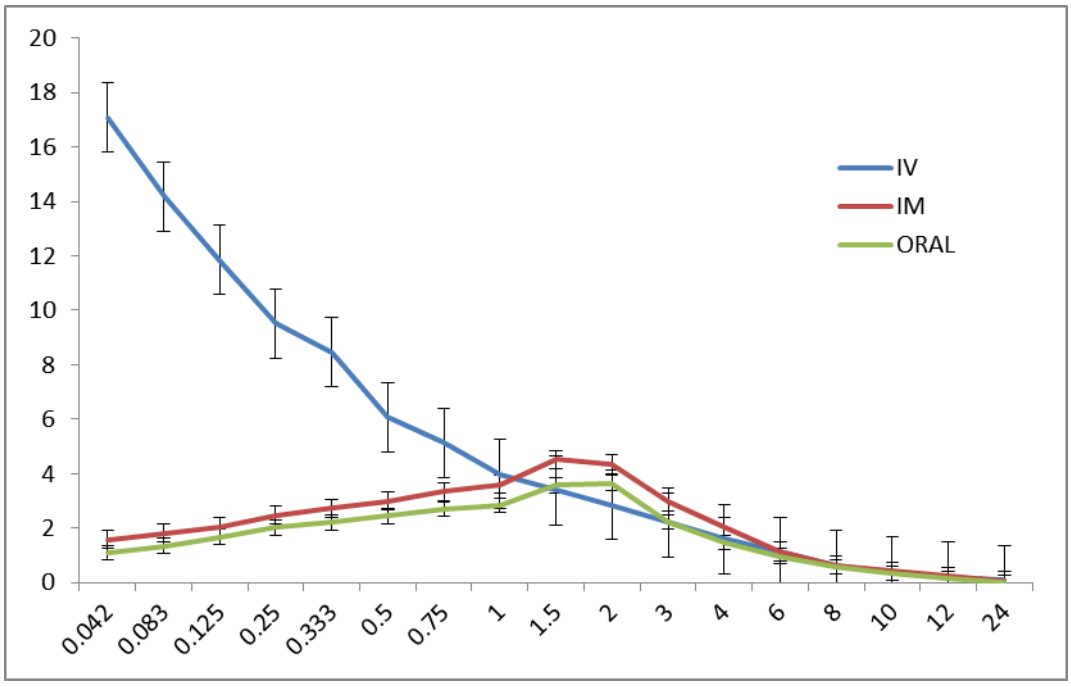

Fig 1: Concentration (Mean±S.E) of enrofloxacin following intravenous (IV), Intramuscular (IM) and oral administration in goats (n=5).

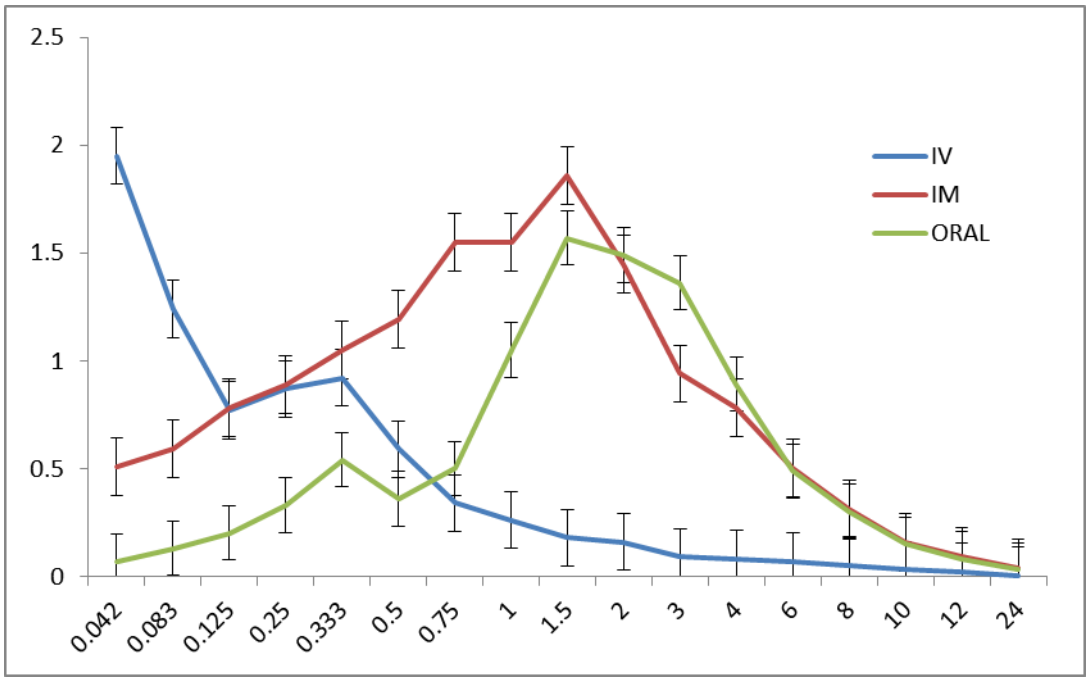

Fig 2: Concentration (Mean±S.E) of Ciprofloxacin (metabolite of enrofloxacin) after intravenous (IV), intramuscular (IM) and oral administration in goats (n=5).

Conclusion

This study compared the IV, IM and oral pharmacokinetic characteristics of enrofloxacin in goats, to the best of our knowledge. Enrofloxacin demonstrated adequate pharmacokinetic characteristics, including elimination half-life ($t_{1/2}\beta$), MRT, T_{max} and greater bioavailability when administered through intramuscular injection (IM) at a dosage level of 5 $mg.kg^{-1}$ body weight. For the IV and IM routes, the predicted dosage regimens (D* and D_0) were found to be non-significant. Although the doses (D* and D_0) for the oral route are substantially larger. More than 12 hours after a single intravenous, intramuscular and oral injection, respectively, the medication maintained its therapeutic concentration (≥ 0.125 $\mu g.ml^{-1}$). Enrofloxacin also has the advantage of being converted into ciprofloxacin, which has a favourable pharmacokinetic profile and the potential to exert antibacterial action at very low concentrations. Enrofloxacin is thus anticipated to be equally effective when administered intravenously, intramuscularly and orally for the treatment of both systemic and local infections in goats at a dose rate of 5 $mg.kg^{-1}$ body weight twice daily.

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