Kinetics of Enrofloxacin in Goat Following Intravenous and Intramuscular Administration

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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, respectively. 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 area under curve was more after IM administration than by IV administration, suggesting that IM route could be better off in maintaining a prolonged plasma concentration of the drug.

Key Words: Pharmacokinetic, enrofloxacin, goat.

Introduction:

Flouroquinolones (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). Flouroquinolones 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 orbifloxaacin 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; Barrierc *et al*., 1987; Nouws *et al*., 1988; Walker *et al*., 1990; Andriole, 1993). Published pharmacokinetic data of enrofloxacin in goat are scarce and difficult to compare because of the different breeds of goat, administration procedures or analytical methods are used. Thus, the aim of the present study was to elucidate some of pharmacokinetic parameters of enrofloxacin in healthy Ardi 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 × g for 5 min. Serum was separated and stored at –20 ^{o}C until analysis. Concentration of the drug in the serum was determined spectrophotometrically by the method of Jha *et al*. (1996). The absorbance maxima of enrofloxacin were recorded at 278 nm. Sensitivity of

the assay was 0.005 μg. 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 $F = AUC_{i.m.} / AUC_{i.v.}$.

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 μg/ml. Mean volume of the central compartment (1.5 l/kg) and volume of distribution at steady state (3.1 l/kg) were high. The rate of distribution from the central to the peripheral compartment and vice versa was equal.

Enrofloxacin concentration versus time curves was generated from data obtained after IM administration (Fig. 1). The 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 μg/ml was achieved in 0.74 h. Volume of distribution was similar but AUC was greater after IM than IV.

Discussion:

Pharmacokinnetics of enrofloxacin in goats are similar to others reported elsewhere (Rao *et al*., 2000; 2001; 2002; Elsheikh *et al*., 2002). The spectrophotometric method used in this study could also measure metabolites. Other studies were also performed in 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*., 1999; Bregante *et al*., 1999; Heinen, 2002; Papich *et al*., 2002). 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 *et al*., 1996; Walker**,** 2000; Rao *et al*., 2002). Indicating extensive pentration into tissues. The rate of distribution from central to peripheral was equal, indicating that the drug likely moves rapidly from the extracellular fluid into cells and vice versa. 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.

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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 ± SD**
C_{max} (μg/ml)	0.88 ± 0.21
A (μg/ml)	0.61 ± 0.10
α (h^{-1})	1.47 ± 0.25
$t_{1/2}$ (α) (h)	0.56 ±0.02
B (μg/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 (μg/ml/h)	2.23 ± 16
Cl_B (L/kg/min)	o.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} toK_{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 ± SD
C_{max} (μg/ml)	0.33 ± 0.02
AUC (μg/ml/h)	2.29 ± 0.12
Kabs (h^{-1})	5.90 ± 1.02
$t_{1/2}$ abs (h^{-1})	0.15 ± 0.02
Kel (h^{-1})	0.16 ± 0.02
$t_{1/2}$ el (h)	4.41 ± 0.12
F (%)	110 ± 9.8

C_{max} = peak concentration; $t_{1/2}$ (α) = half-life of distribution phase; AUC = area under the concentration-time curve Kabs = absorption rate constant; $t_{1/2}$ abs = absorption half-life; Kel = tissue fluid elimination rate constant; $t_{1/2}$ el = tissue fluid elimination half-lif; F = biovaibility.

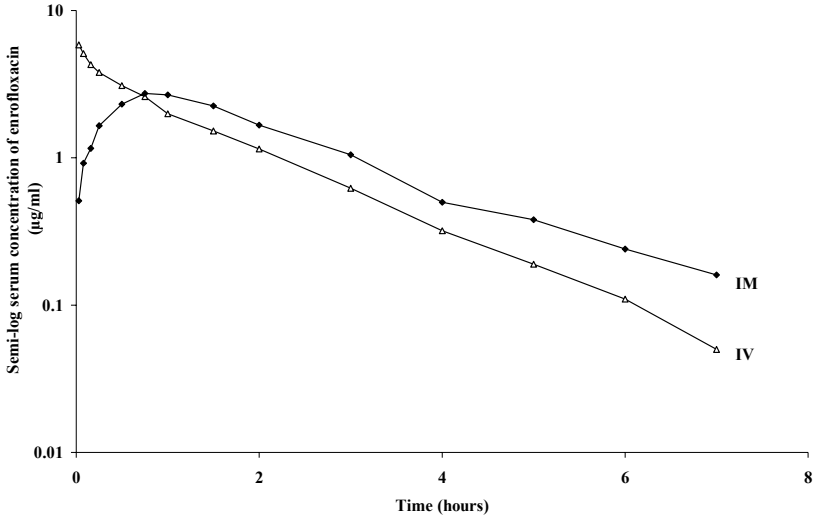

Fig 1: Mean semi-log serum concentrations of enrofloxacin versus time following a single IV and IM dose of 5 mg/kg body weights to healthy goats. (n. = 5 each).

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الحرائك الدوائية للانروفلوكساسين في الماعز بعد حقنها في الوريد والعضل

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قسم وظائف الاعضاء والكيمياء الحيوية والاقربازين

كلية الطب البيطري والثروة الحيوانية - جامعة الملك فيصل

الاحساء - المملكة العربية السعودية

الملخص:

تم قياس الحرائك الدوائية للانروفلوكساسين في الماعز بعد حقنها بالوريد والعضل بجرعة مقدارها ٥ ملجرام لكل كيلوجرام. تبين ان الدواء يطابق نظام موديل التوزيع في حيزين، حيث عمر النصف حوالي ٤,٧ ساعة عندما اعطي الدواء في الوريد و ٤,٤ ساعة عندما اعطي في العضل. لقد كان تركيز الدواء في السيرم في مستوى علاجي ولمدة ٩ و ١٢ ساعة بعد الحقن الوريدي والحقن العضلي بالتتابع. لقد كان حجم توزيع الدواء كبيراً بعد الحقن بكلا الطريقتين.