Research Article

Pharmacokinetics of Ciprofloxacin and Dosage Regimens for Calves

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ABSTRACT

Objective: The determine the pharmacokinetics and suggest rational dosage regimens of ciprofloxacin for calves. **Methods**: Ciprofloxacin was administered to five calves intravenously (IV) at the dose level of 5 mg/kg body weight. Plasma concentrations of the test drug were estimated by using spectrofluorimetric assay method. The pharmacokinetic parameters were determined by using compartmental model and model-independent methods based on the statistical moment theory. Common pharmacokinetic determinants from both the methods were compared statistically and the dosage regimens of ciprofloxacin for calves were computed. **Results:** Plasma ciprofloxacin concentrations at various time intervals declined in a biphasic way, initially rapidly from 5.71±0.63 µg/ml at 0.04hr to 3.06±0.35 µg/ml at 0.75hr and thereafter gradually to 0.35±0.18 µg/ml at 6hr. The pharmacokinetic profile of ciprofloxacin was generated following two-compartment open model. The values of $t_{½}$, $t_{½}$, $Vd_{area,}$ AUC and Cl_B were calculated to be 0.31+0.02 hr, 2.69+0.58 hr, 1.71±0.44 L/kg, 11.64±1.55 µg/ml.hr and 454...32±59.21 ml/kg/hr, respectively. The distribution and elimination characteristics of ciprofloxacin based on non compartmental model were not significantly different from those reported for compartment model. **Conclusion:** Based on the pharmacodynamic properties of the test drug and its post –antibiotic effect and the pharmacokinetic data of ciprofloxacin data of ciprofloxacin in calves, it may be administered @ 5 mg/kg body weight at 24 hr interval by intravenous route. However, for more severe infections it may be administered at the dose rates of 4.5 and 3.2 mg/kg body weight as the loading and maintenance doses, respectively and repeated at 6 hr intervals.

Keywords: pharmacokinetics, ciprofloxacin, calves, dosage regimen.

INTRODUCTION

Fluoroquinolones, the synthetic broad spectrum bactericidal agents, are gaining wide spread acceptance in veterinary medicine as these are extremely active even at very low concentration against a broad spectrum of microorganism including gram-negative and gram-positive bacteria, even those which are resistant to aminoglycosides. Antipseudomonal penicillins and third generation cephalosporins, Mycoplasma, Chlamydia, Rickettsia, Mycobacteria species, Plasmodium species, Treponema cruzi and Leishmania species. These are becoming very popular in veterinary clinical practical to treat urinary tract, respiratory tract, gastrointestinal tract, skin and soft tissue infections.

Pharmacokinetic data of ciprofloxacin has been generated in sheep, goats, preruminant calves and pigs, horses and dogs. Keeping in view the large differences in disposition kinetic behavior of drugs in different species of animals and also age, assay, methods and pharmacokinetics evaluation with compartment and non-compartment models, present study with undertaken to investigate the disposition kinetics of ciprofloxacin following a single intravenous administration in calves and to establish a rational and suitable dosage regimen schedule for calves in view of the pharmacodynamic-pharmacokinetic relationship of this antimicrobial agent.

MATERIALS AND METHODS

Five healthy female Hariana cross-bred calves aging between 6 and 11 months and weighing 43 to 73 kg available in the farm of this institute were used in the present study. The animals were maintained under standard feeding and managemental conditions. The animals had free access to feed and drinking water.

Ciprofloxacin treatment and assay

Technical grade ciprofloxacin base was procured from reputed company. Drug solution of 3% strength was prepared freshly and injected into the external jugular vein of animals at the dose of 5 mg/kg body weight. Blood samples were collected at pre-determined time intervals of 0.04, 0.08, 0.16, 0.25, 0.50, 0.75, 1, 2, 3, 6,9, 12, 24, 36, 48 and 72 hr after drug administration into heparinised test tubes. Plasma samples were separated and stored at -20°C until analysis following spectroflourimetric assay method using shimadzu RF 5000 spectroflurometer .

Pharmacokinetic analysis

Plasma concentration of ciprofloxacin versus time profile of each animal were used to determine the disposition kinetic variables using compartmental model and non compartmental pharmacokinetic model based on the statistical moment theory. Area under the plasma concentration- time curve(AUC) and the area under the moment curve (AUMC) were determined using trapezoidal method. Other pharmacokinetic parameters were derived using the following equations:

Mean residence time (MRT) = AUMC/AUC

Overall elimination rate constant (K_{el}) = 1/MRT

Biological Half Life ($t_{1/2}$) = 0.693 X MRT

Total body clearance (CL) = dose/AUC

Volume of distribution at steady state (Vd_{ss}) = MRT X CL

Predicted steady state plasma concentration of drug with 24 hr as the dosing interval (x) $=AUC_{a/x}$

The pharmacokinetic data derived by compartmental and non compartmental analysis methods was compared statistically applying the student 't' test.

RESULTS

Plasma ciprofloxacin concentrations (mean+SEM)- time curve following a single intravenous of 5mg/kg body weight in cow calves is shown in figure 1. Mean plasma concentration of the drug was found to be 5.71+0.63 µg/ml at 2.5 min which rapidly declined to 3.06±0.35 µg/ml at 0.75 h and thereafter gradually to 0.35µ g/ml at 6 hr(fig 1). The plasma ciprofloxacin concentration versus time data was best fitted to a biexponential equation corresponding to a two-compartmental open model. The distribution and elimination phase regression lines were determined by least square regression methods and are shown in fig 1. The simulated curves of ciprofloxacin concentrations in the central and tissue compartments as a function of time and the fraction of dose eliminated from the central compartment were determined according to a two-compartment open model and are shown in fig2.

The compartmental and non-compartmental pharmacokinetic parameters (mean±SEM) after intravenous administration of the test drug in calves are presented in table 1. Following compartmental model, the distribution and elimination half-life of ciprofloxacin in calves was found to be 0.13 and 2.69hr respectively. The Vd_{area} , AUC and Cl_B values were calculated to be 1.71±0.44 L/Kg, 11.64±1.55 µg/ml.hr and 454.32± 59.21 ml/kg/hr, respectively. Further, the values of $k_{12}/k_{21}$and the ratio of the drug concentration between the tissue and central compartment (T/C) were 0.72 and 1.14, respectively.

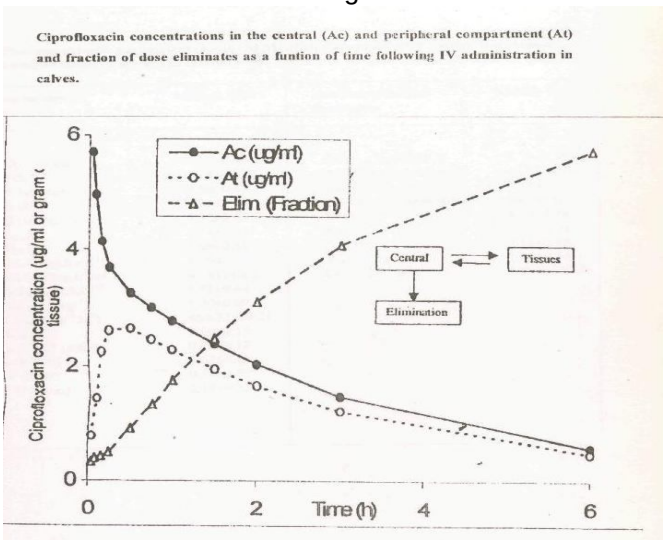
The disposition kinetic parameters of ciprofloxacin in calves on the non-compartmental model of analysis are also listed in table. The values of biological half-life ,AUC, VD_{SS} and MRT for ciprofloxacin were found to be 3.18 h,8.74

µg/ml.hr, 1.70 L/kg and 4.59hr respectively.

Pharmacokinetic parameters (mean+SEM) of ciprofloxacin after a single intravenous administration (5mg/kg) in calves (n=5)

Compartmental	Mean ± SEM	Noncompartmental parameters	Mean ± SEM
Cp^0 (µg/ml)	6.81±0.94		
a (h^{-1})	10.85±3.37		
A (µg/ml)	3.50±0.67		
B (h^{-1})	0.31±0.06		
B (µg/ml)	3.32±0.57	AUC_{0-1}(µg.h-ml-1)	8.74±1.45
$t_{½a}$ (h)	0.13±0.02	$AUMC_{0-1}$(µg-h2ml-1	15.61±4.16
$t_{½b}$ (h)	2.69±0.58	AUC_{0-00} (µg.h2.ml-1)	13.14±2.53
AUC (pg.h.ml^{-1})	11.64±1.55	$AUMC_{0-00?}$(µg-h2ml-1)	70.29±31.11
AUMC(µg.h^2.ml^{-1})	43.81±10.37	MRT (h)	4.59±1.28
$Vd_{(area)}$(LKG^{-1})	1.71±0.44	K (h^{-1})	0.29±0.07
$Vd_{(ss)}$ (LKg^{-1})	1.30±0.09	$t_{½k}$(h)	3.18±0.88
$Cl_{(b)}$ml.kg^{-1}.h^{-1}	454.32±59.21	$Vd_{(ss)}$ (Lkg^{-1})	1.70±0.34
K_{10}(h^{-1})	0.64±0.15	Cl(ml.kg^{-1} h^{-1})	423.76±57.76
K_{12}/K_{21} (ratio)	0.72±0.17		
MRT (h)	3.62±0.65		
fc (ratio)	0.51±0.07		
T/P (ratio)	1.14±0.32		

Ciprofloxacin concentrations in the central (Ac)and peripheral compartment(At) and fraction of dose eliminates as a function of time following IV administration in calves.



DISCUSSION

Following intravenous administration, mean(±SEM) plasma ciprofloxacin concentration versus time data in calves were best fitted to a two compartment open model. This is in agreement with the results of other studies in sheep, goats, pre-ruminant calves and dogs.

Keeping in view the growing emphasis on model-independent pharmacokinetic analysis due to certain limitations and bias of the compartmental methods, determined the deposition kinetic variables based on compartmental and non-compartmental models for ciprofloxacin in the present study. But no data are available on the model-independent pharmacokinetic analysis of ciprofloxacin in animals.

Based on distribution and elimination rate constants and the transfer rate constants of the drug from the central to peripheral compartment and vice-versa, the relationship of ciprofloxacin concentration

in the central and peripheral compartments along with its elimination from the central compartment were determined which revealed that therapeutically satisfactory concentration of the drug could be achieved in the tissues within 5min of the drug administration and maintained up to 6 hr and ciprofloxacin has the tendency to stay in slightly higher concentration in the central compartment compared to the peripheral compartment.

Based on compartmental model, the distribution half life ($t_{½a}$) of ciprofloxacin in calves after IV administration was found to be 0.13 hr which suggests rapid distribution of the drug into body tissues and fluids. Distribution half life of ciprofloxacin in calves in the present study (7.8min) was longer than that of 2.38 min in sheep, 2.4 to 3.15 min in dogs but was shorter than that in pigs-ruminant calves.

The elimination half life ($t_{½B}$) of ciprofloxacin in calves in the present study (2.69 h) is almost comparable to that of 2.44 hr in pre-ruminant calves but longer compared to 1.2 hr in sheep and shorter than that of 4.85 hr in horses. The apparent volume of distribution $Vd_{(area)}$ of >1.0 L/kg suggests substantial tissue penetration of the drug. The volume of distribution values ($Vd_{(area)}$, Vd_B, Vd_{ss}) of 1.30 to 1.91 L/kg in calves were of course markedly lower compared to that of 1.89 L/kg in sheep. High AUC value of 11.64±1.55 µg±1.55 µg/ml.hr of ciprofloxacin in calves also adds credence to the fact that this antibacterial agent widely distributes in body fluids and tissues of calves and thus can be effectively used for the treatment of various systemic including deep seated infections.

Almost 50 percent of the drug in the central pool (fc;0.5±0.07) and ratio of transfer rate constants of ciprofloxacin from central to peripheral compartments and vice-versa (K_{12} /K_{21}; 0.72)suggest that this drug does not has much tendency to accumulate in body tissue, and thus less likely to adversely affect the human or animal health due to drug residues.

Statistical comparison of certain selected pharmacokinetic parameters like-$t_{½B}$, AUC, Vd_{ss}, Cl_B and MRT derived from compartmental and non-compartmental models revealed no significance differences in the disposition kinetic variables. Thus, suggesting that if appropriate pharmacokinetic model is applied without any prejudice, then the compartmental model is as accurate, reliable and effective as the model-independent analysis.

Fluoroquinolones exert concentration-dependent bacterial effect. To maximize their clinical efficacy, it is important to obtain a plasma C_{max} to MIC ratio (C_{max}/MIC) of 8-12

Bacterial regrowth due to resistant-sub-populations can be prevented when peak concentration of fluoroquinolones exceed the MIC values of pathogens by a factor of 8 or more. Considering the MIC values of 0.5µg/ml against most of the susceptible pathogens, the C_{max}/MIC ratio of ciprofloxacin in calves in the present study was found to be 11.42. Therefore, plasma ciprofloxacin levels after intravenous administration in calves in the present study revealed that a dose of 5 mg/kg is sufficient to provide therapeutically satisfactory concentration for almost 6hr.

However in view of the concentration-dependent killing effect, its post-antibiotic effect and the pharmacodynamic-pharmacokinetic relationship (C_{max}/MIC) values of 11.42, it may not be unreasonable to suggest that ciprofloxacin may be administration to calves at 24 hr interval by intravenous route. However, for more severe infections requiring higher plasma concentration (>1.0µg/ml), ciprofloxacin may be administered at the dose rates of 4.5 and 3.2mg/kg body weight as the loading and maintenance doses, respectively and be repeated at 6hours interval.

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