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Comparative Disposition Kinetics and Bioavailability of Ofloxacin after Extravascular Administration in Buffalo (*Bubalus bubalis*) Calves

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Abstract

Comparative disposition kinetics of ofloxacin was studied in buffalo calves following its Intramuscular (IM) and Subcutaneous (SC) administration @ 5 mg/kg body weight. Plasma ofloxacin concentrations were determined by microbial assay method using *E. coli* as test organism. Ofloxacin could be determined in plasma within 2.5 min of drug administration and peak levels of 2.37 ± 0.06 and 2.20 ± 0.02 µg/ml were observed at 0.75 and 1.0 h after IM and SC administration, respectively. Blood levels of around 0.25 µg/ml were observed for up to 24 h and pharmacokinetics was best described by two-compartment open model following both the routes. Absorption and elimination half life values were found to be 0.14 ± 0.02 and 22.88 ± 81.97 h after IM administration while 0.18 ± 0.04 and 28.25 ± 2.04 h after SC administration. The AUC values after IM and SC administration were calculated to be 24.99 ± 0.95 and 28.24 ± 0.65 µg.h/ml, respectively while respective bioavailability values were found to be 116.23 ± 8.03 and 107.10 ± 10.22 per cent indicating almost complete absorption of ofloxacin following administration by either of the routes. Based on the efficacy predictor values, ofloxacin be administered to buffalo calves @ 5 mg/kg by IM or SC route and be repeated at 24 h interval. However, for bacterial isolates requiring higher drug concentrations, ofloxacin be administered at 7.5 mg/kg and be repeated at 12 h interval. Further, preferential use of SC route over IM route is recommended for ofloxacin administration to buffalo calves.

Keywords: Pharmacokinetics; Buffalo calves; Bioavailability; Intramuscular; Subcutaneous

Introduction

Fluoroquinolones are highly effective broad-spectrum antimicrobial agents and have maintained high antibacterial activity against susceptible pathogens over the years [1 as the microbial resistance to their action does not develop rapidly [2]. These are widely distributed in body and their concentrations in target tissues are significantly higher than in blood [3,4]. Therefore, these revolutionized the therapeutic armamentaria in human and veterinary clinical practice against bacterial pathogens, especially those which are resistant to traditionally used antibacterial agents, including beta lactam antibiotics, aminoglycosides, third generation cephalosporins, tetracyclines, macrolides and sulfonamides etc. [5-7].

Ofloxacin, a fluorinated quinolone carboxylic acid derivative, is effective against gram-positive and gram-negative bacteria, Mycoplasma and Rickettsiae, required in very low concentrations (0.03-0.50 µg/ml) against common pathogens of animals [8] and is generally very safe and thus can be employed for treating the gastrointestinal, respiratory, urino-genital, skin and other systemic inflections of animals [6,7].

Pharmacokinetic studies of ofloxacin following different routes of administration in rabbits [9], dogs [10], pigs [11], goats [12], chickens [13,14] and neonatal calves [15,16] have revealed species- and age-dependent differences in pharmacokinetic profile. Disposition kinetics of ofloxacin has also been studied in buffalo calves following intravenous [17,18] and after intramuscular administration [19]. But no comparative data are available on its disposition kinetics following Intramuscular (IM) and Subcutaneous (SC) administration in this species. Therefore, present study was undertaken especially to determine the comparative bioavailability and suggest the rational dosage regimens based on Pharmacokinetic (PK) and Pharmacodynamics (PD) integration for its safe therapeutic use in buffaloes.

Materials and Method

Five healthy female Murrah buffalo *(Bubalus bubalis)* calves aging between six and eight months and weighing from 48-60 kg were procured from Dairy Farm of the Institute and maintained under standard managemental conditions. The calves were offered *ad libitum* seasonal green fodder and wheat straw. Concentrate was also provided as per requirement and the animals had free access to drinking water.

Ofloxacin (Technical grade, 99.6% purity; Ranbaxy Research Laboratories, India) was dissolved in 0.1 N hydrochloric acid to prepare 5.0 per cent stock solution (w/v) of the drug which was further diluted to 3.0 per cent strength (w/v) using sterile water for injection immediately before administration. Freshly prepared drug solution was injected at the dose rate of 5 mg/kg body weight by Intramuscular (IM) and Subcutaneous (SC) routes on lateral aspect of the neck at an intervening period of more than 21 days between two administrations. Blood samples were collected from catheterized jugular vein in to heparinized test tubes before injecting ofloxacin (0 h) and at 0.04, 0.08, 0.17, 0.25, 0.33, 0.50, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96

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and 120 h after drug administration. Plasma was separated and stored at -20°C until assayed.

Plasma ofloxacin concentrations were quantified employing the modified agar diffusion microbiological assay method [20] using *Escherichia coli* (A TCC 25922) as the reference organism. All the standards and test samples were assayed in triplicate and the mean of these replicates was determined. The minimum quantification limit of the employed assay procedure was 0.08 µg/ml as reported earlier [16].

Based on the apparent visual curve fitting of semi-logarithmic plots of plasma ofloxacin concentrations versus time data of individual animals following administration by IM and SC routes, pharmacokinetic determinants were determined. Plasma ofloxacin levels-time data after attainment of peak levels were best fitted to a two-compartment open model with the first order absorption using the bi-exponential equation:

$Cp = (Ae^{-\alpha t} + Be^{-\beta t}) Ae'^{-Kat}$;

Where K_a, α and β are absorption, distribution and elimination rate constants; A', A and B are the zero time intercepts of absorption, distribution and elimination phases, respectively; and "e" is base of the natural logarithm.

The rate constants, so derived, were used to calculate the respective half life values. Other pharmacokinetic parameters were computed according to the standard formulae [21,22]. Values of all the pharmacokinetic parameters have been expressed as the mean ± SE.

Results and Discussion

Plasma ofloxacin concentrations versus time data following single IM and SC administration in buffalo calves is illustrated in Figure 1. Absorption of the drug from IM and SC sites appeared to be very fast as 0 .19 µg/ml of ofloxacin could be detected in plasma with in 2.5 min of drug administration by either of the routes. Peak plasma levels of ofloxacin were found to be 2.37 ± 0.06 µg/ml and 2.20 ± 0.01 µg/ml at 0.75 and 1.0 h, after IM and SC administration, respectively (Figure 1). After peak levels, plasma levels initially declined moderately to 1.22 ± 0.08 and 1.22 ± 0.04 µg/ml at 4 h and thereafter gradually to 0.18 ± 0.01 and 0.20 ± 0.00 µg/ml at 36 h as shown in (Figure 1). Although ofloxacin could be detected in plasma up to 36 h, but concentrations around the MIC value of 0.25 µg/ml were observed up to 24 h only.

Plasma ofloxacin concentrations versus time data in buffalo calves was best described by two-compartment model after attaining the maxima following extravascular (IM/SC) administration. But disposition of ofloxacin in buffalo calves has been described by two-compartment model [17] and by three compartment open model [18] after IV administration while by one compartment open model after IM administration [19] and by two-compartment open model in rabbits [9], chickens [13] and neonatal cow calves [15] and model-independent methods in dogs [10], pigs [11] and chickens [14] .

Disposition kinetic determinants of ofloxacin in buffalo calves following IM and SC administration are summarized in Table 1. Following IM and SC administration, absorption of ofloxacin was apparently very fast as revealed by initial plasma drug concentrations with in 2.5 min of drug administration (Figure 1) and also the respective absorption half life (t_{1l2Ka}) values of 0.14 and 0.18 h and the t_{max} values of 0.75 and 1.0 h (Table 1). Almost similar $t_{l/2Ka}$ values (0.12-0.23 h) have been reported after IM and SC administration in neonatal calves [16]. Therefore $t_{l/2Ka}$ values after IM or SC injection suggest its rapid absorption in buffalo calves. After attainment of peak levels (C_{max}), a distinctive phase of drug distribution was observed. Similar pattern of absorption and distribution of ofloxacin has been reported following IM and SC administration in neonatal calves too 16.

Elimination half-life of ofloxacin in buffalo calves in the present study was found to be 22.88 and 28.25 h following IM and SC administration, respectively (Table 1). Elimination half-life of ofloxacin in buffalo calves following extravascular administration was several folds higher compared to 4.82 h in chickens [13,14], 1.59 h in rabbits [9] and 1.96 h in dogs [10] and marginally higher than 18.62 and 19.80 h, respectively after IM and SC administration in neonatal calves [16]; thus suggesting that buffalo calves are slow eliminators compared to other species.

The AUC values of ofloxacin in buffalo calves after IM and SC administration were calculated to be 24.99 ± 0.95 and 28.24 + 0.65

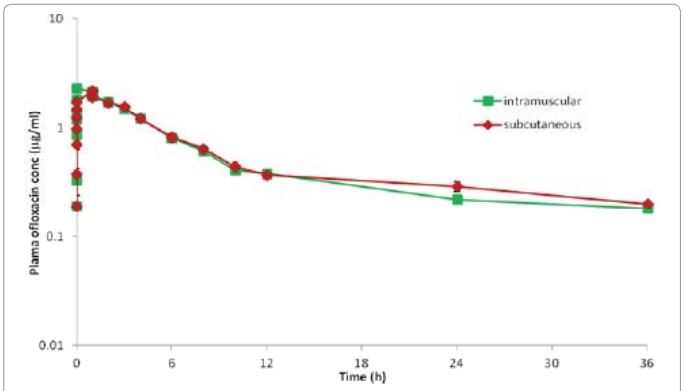

Figure 1: Semilogarithmic plot of the comparative mean plasma ofloxacin concentrations- time profile following a single im and sc administration @ 5 $mg.kg^{-1}$ in buffalo calves. Data presented are mean ± SE of five animals.

Parameters (units)	Routes of administration	
	Intramuscular	Subcutaneous
A' ($\mu g.ml^{-1}$)	3.17 ± 0.58	2.92 ± 0.44
K_a (h^{-1})	5.51 ± 0.98	4.44 ± 0.74
$t_{1/2ka}$ (h)	0.14 ± 0.02	0.18 ± 0.04
A ($\mu g.ml^{-1}$)	2.24 ± 0.14	2.16 ± 0.09
α (h^{-1})	0.27 ± 0.03	0.25 ± 0.01
$t_{1/2\alpha}$ (h)	2.64 ± 0.32	2.80 ± 0.17
B ($\mu g.ml^{-1}$)	0.53 ± 0.03	0.51 ± 0.04
β (h^{-1})	0.03 ± 0.00	0.03 ± 0.00
$t_{1/2\beta}$ (h)	22.88 ± 1.97	28.25 ± 2.04
$C_{max(obs)}$ ($\mu g.ml^{-1}$)	2.37 ± 0.06	2.20 ± 0.02
$t_{max(obs)}$ (h)	0.75 ± 0.00	*1.00 ± 0.00
AUC ($\mu g.ml^{-1}h$)	24.99 ± 0.95	*28.24 ± 0.65
AUMC ($\mu g.ml^{-1}h^2$)	601.85 ± 59.90	**859.29 ± 60.33
MRT (h)	24.02 ± 2.0	*30.41 ± 2.00
F (%)	116.23 ± 8.03	107.10 ± 10.22

*P < 0.05, **P < 0.01

A' - zero time intercept of the least square regression line of the absorption phase; A - zero time intercept of the least square regression line of the distribution phase; α - distribution rate constant; β - The overall elimination rate constant; B - zero time intercept of the elimination phase; $t_{1/2ka}$ - absorption half-life; $t_{1/2\beta}$ - elimination half-life; K_a - absorption rate constant; AUC - total area under the plasma drug concentration time curve; AUMC - total area under the first moment of plasma drug concentration time curve; MAT- mean absorption time; MRT - mean residence time; $C_{max(obs)}$ - observed peak plasma concentration of the drug; $t_{max(obs)}$ - time period at which the peak plasma concentration is observed; F – bioavailability.

Table 1: Pharmacokinetic determinants (mean ± SE) of ofloxacin following a single IM and SC administration (5 $mg.kg^{-1}$) in buffalo calves.

μg.h/ml, respectively. Almost similar higher values of AUC of ofloxacin have been reported in neonatal calves [15,16] but these were shorter than in rabbits after IV or SC administration [9] , oral administration in dogs [10 and IV administration in chickens [13].

Systemic availability of ofloxacin in buffalo calves after IM and SC administration were calculated to be 116.23 ± 8.03 and 107.10 ± 10.22 per cent, respectively which indicate almost complete absorption of ofloxacin from the site of injection. No data are available on bioavailability of ofloxacin in buffalo calves or any other species of animals after IM administration, therefore, difficult to compare across the species. However, its bioavailability in buffalo calves was almost comparable to other fluoroquinolones after parenteral administration in pre-ruminant and ruminant cattle [7].

Certain efficacy predictor indices have been evolved and unequivocally accepted for concentration-dependent antibacterial agents including fluoroquinolones. For successful outcome of therapy, high C_{max}/MIC values of 8-12 [23,24] and AUC to MIC ratio (AUC/MIC) value of > 100 are necessary for avoiding bacterial resistance emergence [23,25-27]. In the present study, we did not determine the MIC values of ofloxacin against any microbe but considering the MIC value of ofloxacin as 0.25 μg/ml against some of the sensitive isolates of veterinary clinical significance [8,28] and the observed C_{max} values after IM and SC administration, the respective C_{max}/MIC and AUC/MIC values were found to be 9.48, 96.06 and 8.80 and 112.96, respectively after IM and SC injections. All the efficacy predictors were almost equal to or higher than the desired values of 8-12 and > 100 for C_{max}/MIC and AUC/MIC, respectively. Therefore, based on the efficacy predictor values obtained in the present study, it may be suggested that ofloxacin be administered to buffalo calves at the dose level of 5 mg/kg by IM or SC route and be repeated at 24 h interval. However, for the isolates requiring higher antibacterial concentrations, the drug should be administered at higher dose level, may be 7.5 mg/kg and/or be repeated at 12 h interval. Further, preferential use of SC route over IM route for ofloxacin in buffalo calves is also recommended for obvious reasons as has been suggested for gentamicin [29], amikacin [30] and sulfamethoxypyridazine in goats [31].

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