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# Pharmacokinetics and bioavailability of ofloxacin following single intramuscular and subcutaneous administration in goats

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Fluoroquinolones revolutionized the therapeutic armamentaria against bacterial pathogens, especially those which are resistant to traditionally used antibacterial agents, including beta-lactam antibiotics, aminoglycosides, third generation cephalosporins, tetracyclines, macrolides, sulphonamides etc. (Mckellar 1996). These are highly effective broad-spectrum antimicrobials (Karlowsky *et al*. 2002), widely distributed in body and their concentrations in target tissues are significantly higher than in blood (Intorre *et al*. 1997) and microbial resistance does not develop rapidly (Hooper 2000). Therefore, these are extensively used both in human and veterinary clinical practices.

Ofloxacin, a fluorinated second generation quinolone, is rapidly absorbed and has good oral bioavailability (80 to 90%), little biotransformation in liver, low plasma protein binding, high volume of distribution and undergoes almost complete elimination in unchanged form through urine (80% in 24 h). Minimum inhibitory concentration ($MIC_{90}$) values of the ofloxacin against some of the common isolates of veterinary importance range between 0.06 and 0.5 µg/ml (Greene and Budsberg 1993). Disposition kinetics of ofloxacin following different routes of drug administration was studied in dogs (Yoshida *et al*. 1998), pigs (Son *et al*. 2000), goats (Baruah *et al*. 2004) and neonatal calves (Gaur *et al*. 2004, 2005). However, comparative pharmacokinetic data on ofloxacin following i.m. and s.c. administration are lacking in goats, therefore, the present study was undertaken.

Healthy female Barberi goats (5), 1.2 - 2.0 year-old and weighing 18–22 kg, were dewormed using fenbendazole (5 mg/kg) 21 days before the start of experiment. A washout period of 21 days was allowed between 2 ofloxacin treatments (i.m. and s.c.). The experimental protocol was approved by Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA) on the recommendation of Institutional Animal Ethics Committee (IAEC).

Ofloxacin was administered @ 10 mg/kg body weight into neck muscles or in the subcutaneous space on lateral aspect of neck at an intervening washout period of 21 days. Blood samples were collected into heparinised tubes from jugular vein at 2.5, 5, 10, 15, 30, 45 minutes and 1, 1.5, 2, 3, 6, 8, 12, 18, 24, 30, 36 and 48 h after drug administration. Blood samples were centrifuged at 3,000 rpm for 20 min and plasma was separated and stored at –20 °C until assayed. Oflaxacin extraction from plasma was carried out as per Neilson and Gyrd-Hansen (1997) with certain modifications. In 0.5 ml plasma, 0.5 ml acetonitrile was added and the mixture was vortexed for 1 min at high speed and centrifuged at 9,000 rpm for 10 min. The clear supernatant (0.5 ml) was collected in a micro-centrifuge tube and 0.5 ml of HPLC grade water was added to it and the mixture was filtered through 0.22 µm cellulose acetate membrane filter.

Ofloxacin levels in plasma were determined using the modified HPLC method of Gao *et al*. (2007) for levofloxacin using $C_{18}$ reverse phase column (particle size 5 µm; 4.6 mm × 250 mm), photodiode array detector with empower software. Mobile phase consisted of acetonitrile, water, phosphoric acid and triethylamine (15: 84: 0.5: 0.60, v/v) with 2.3 pH. Detection wavelength was set at 295 nm. 20 µl sample was injected at a mobile phase flow rate of 1.50 ml/min at an ambient temperature of 25.0±0.5°C. Retention time of ofloxacin was 6.90±0.1 min. Stock solution (100 µg/ml) of ofloxacin was prepared in 0.1 N NaOH. Standard curve of ofloxacin was linear in the concentration range of 0.05 to 3.20 µg/ml and the correlation coefficient ($R^2$) value was 0.999.The intra-day and inter-day coefficients of variance were less than 10% and the mean recovery was more than 90%.

Kinetic parameters were determined with an iterative least square non-linear regression programme using a software and other parameters were determined as per Baggot (1977). Data were expressed as mean±SE except

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$t_{½Ka}$ and $t_{½\beta}$ which were expressed as harmonic mean values. The data were subjected to statistical analysis using student's 't' test and dosage regimens of ofloxacin were computed using the pharmacokinetic and pharmacodynamic indices of antimicrobials (Dudley 1991).

Following intramuscular and subcutaneous administration of ofloxacin (10 mg/kg) in goats, mean plasma concentrations of ofloxacin at different time intervals are shown in Fig. 1. Appreciable and clinically effective ofloxacin concentrations of 0.79±0.15 µg/ml and 0.50±0.10 µg/ml were detected within 2.5 min and the peak plasma concentrations of 3.77±0.27 µg/ml and 3.99±0.35 µg/ml were observed at 60 min following i.m. and s.c. administration, respectively, which gradually declined to 0.13±0.03 µg/ml and 0.30±0.06 µg/ml at 8 h after i.m. and s.c. administration, respectively (Fig. 1).

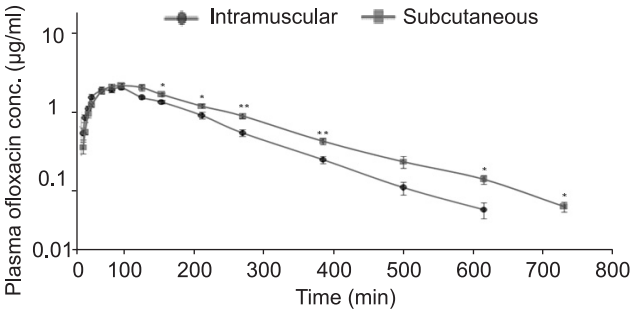


Fig. 1. Semilogarithmic plot of the comparative mean plasma ofloxacin concentrations versus time profile following a single i.m. and s.c. administration @ 10 mg/kg in goats. Data presented are mean±SE of 5 animals. * P < 0.05, ** P < 0.01.

Evaluation of the plasma concentration time profile of ofloxacin following i.m. and s.c. administration revealed that the data could be best fitted to one-compartment open model with first order absorption and were adequately described by the equation:

$$Cp=Be^{-\beta t}-A'e^{-kat}$$

where Cp, plasma concentration of ofloxacin at time t; B and A′, zero time plasma drug concentration intercepts of the elimination and absorption phases; β and $K_a$, elimination and absorption phase rate constants respectively; and e, base of the natural logarithm.

Different pharmacokinetic parameters, determined from plasma levels of ofloxacin following i.m. and s.c. administration in goats, are summarized in Table 1.

Absorption of ofloxacin in goats following extravascular administration (i.m. and s.c.) was very rapid as it could be detected in plasma within 2.5 min of drug administration by either of the routes. Absorption pattern of ofloxacin in goats was almost comparable to that reported in calves (Gaur *et al*. 2005) and plasma concentrations versus time data was best described by one-compartment open model as in neonatal calves (Gaur *et al*. 2005).

Both the absorption (13.59 min) and elimination half-life (78.41 min) values of ofloxacin were numerically lower after i.m. administration than after s.c. administration but these values did not differ significantly from each other. Elimination half life of ofloxacin in goats (1.3 h) after i.m. administration was comparatively shorter than reported in buffalo calves (1.91 h, Kumar *et al*. 2009) and higher than found in neonatal cow calves (0.36 h; Gaur *et al*. 2005) following extravascular administration. Short biological half-life of ofloxacin in goats suggests that goats are fast eliminators than other ruminants.

Table 1. Pharmacokinetic parameters (mean±SE) of ofloxacin following a single i.m. and s.c. administration (10 mg/kg) in goats

| Parameters (units) | Routes of administration | |
|---|---|---|
| | Intramuscular | Subcutaneous |
| B (µg/ml) | 7.18±1.14 | 6.76±0.56 |
| $K_a$ ($min^{-1}$) | 0.05±0.01 | 0.035±0.01 |
| β ($min^{-1}$) | 0.0088±0.00 | 0.0066±0.00 |
| $t_{1/2ka}$ (min) | 13.59# | 17.89# |
| $t_{1/2\ \beta}$ (min) | 78.41# | 103.59# |
| AUC (µg/ml min) | 638.18±27.02 | 860.58±22.31** |
| AUMC | 89697.00± | 133530.7± |
| (µg/ml $min^2$) | 5936.82 | 12272.44* |
| MAT (min) | 54.10±4.47 | 95.86±9.16* |
| MRT (min) | 140.11±5.37 | 181.87±12.03* |
| $C_{max(obs)}$ (µg/ml) | 3.77±0.27 | 3.99±0.35 |
| $T_{max(obs)}$ (min) | 60 | 60 |
| F (%) | 75.43±5.00 | 102.07±7.00** |

#Harmonic mean values;*P<0.05; **P<0.01; 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 was observed; F, bioavailability.

Although AUC value in goats after i.m. administration (638.19±27.02 µg/ml min) was significantly lower than after s.c. administration (860.58±22.31 µg/ml min) but these values were almost similar to those reported in buffalo calves (12.40 µg/ml h, Kumar *et al*. 2009). The values of AUMC and MRT after i.m. administration were significantly (P<0.05) lower compared to the corresponding values after s.c. administration and also the corresponding values of 36.12 µg/ml $h^2$ and 2.90 h in buffalo calves (Kumar *et al*. 2009). These observations corroborate well with fast elimination of ofloxacin in goats.

Bioavailability of ofloxacin in goats following i.m. administration was 75.43% compared to almost 100% (102.07±7.00%) after s.c. administration. Bioavailability of ofloxacin in goats was comparatively higher than in neonatal calves (Gaur *et al*. 2005) where the values of F ranged between 50 and 70% following i.m. and s.c. administration. Further, significantly higher value of F after s.c. administration than after i.m. administration in goats evidently suggests the superiority of s.c. route over i.m. route in goats. Preferential use of s.c. route over i.m. route

has also been suggested for ofloxacin in neonatal calves (Gaur *et al*. 2005).

Fluoroquinolones exert post-antibiotic and concentration–dependent bactericidal effect (Renneberg and Walder 1989) therefore, blood concentrations of these antibacterials are not required to be maintained above the MIC values throughout the duration of therapy. In view of the PK/PD relationship studies and to maximize the clinical efficacy and reduce adverse effects of fluoroquinolones, it is important to achieve the peak plasma concentration to minimum inhibitory concentration ratio ($C_{max}$: MIC) of 8–12 or/and an area under the plasma drug concentration time curve (AUC) and MIC ratio (AUC: MIC) of more than 100 (Dudley 1991); following i.m. and s.c. administration of ofloxacin in goats at the dose rate of 10 mg/kg and considering the MIC value of 0.10 µg/ml (Greene and Budsberg 1993), the $C_{max}$: MIC ratio and AUC: MIC quotients of ofloxacin in goats were found to be 37.7, 39.9 and 106.36, 143.43 h after i.m. and s.c. administration, respectively. Thus based on the results of our study, it is recommended that ofloxacin be administered to goats @ 10 mg/kg at 12 h interval by either of the routes (i.m. and s.c.) and PK parameters suggest superiority of s.c. route over i.m. route for obvious reasons.

## SUMMARY

Comparative disposition kinetics of ofloxacin following intramuscular (i.m.) and subcutaneous (s.c.) administration was studied in goats @ 10 mg/kg. Ofloxacin was determined by HPLC method and kinetic parameters using a software. Appreciable plasma concentrations were observed within 2.5 min of drug administration and peaked at 1 h. $t_{1/2ka}$ and $t_{1/2\beta}$ values were 13.59 and 78.41 min after i.m. administration while 17.89 and 103.59 min after s.c. administration and the corresponding bioavailability values were 75.43±5.00 and 102.07±7.00 %. Ofloxacin may be adiministered to goat @10 mg/kg at 12 h interval by s.c. route.

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