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Research Article

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Pharmacokinetics of pefloxacin in healthy and febrile Ongole calves after single intramuscular administration

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ABSTRACT

Pharmacokinetic study was performed in healthy and febrile Ongole calves following single intramuscular administration of pefloxacin @ 10mg/kg body weight. Febrile condition was induced by injecting Escherichia coli endotoxin @ 1 µg/kg body weight intravenously. The concentration time data of pefloxacin in serum was described by one compartment open model with absorption. The drug was detectable for longer time in healthy calves. Ongole calves exhibited higher bio-availability indicating the complete and rapid absorption of pefloxacin. The peak concentration of the drug in serum of healthy calves was significantly higher than in febrile calves while the time to achieve peak concentration was similar in both groups. The other kinetic parameters like absorption half-life, elimination half-life, MRT, AUC and the duration of therapeutic effect were significantly higher in healthy calves, while absorption half-life was higher in febrile calves. Evaluation of pharmacokinetic variables of pefloxacin in healthy and febrile ongole calves after intramuscular administration elucidated that the drug was metabolised and eliminated at faster rate in febrile calves. Febrile calves exhibited lower values for key kinetic parameters like Cmax, Elimination half-life, AUC and duration of therapeutic effect indicating the requirement of more frequent administration during fever.

Key words: Pefloxacin, Pharmacokinetics, Febrile Ongole calves, Intramuscular,

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INTRODUCTION

Pefloxacin, a synthetic fluoroquinolone antimicrobial agent exhibits extensive distribution and attains high concentrations in the tissues like aortic valve, bone, cardiac muscle, peritoneum, prostate gland and secretions like saliva, sputum and blister fluid [1]. Kinetic data of pefloxacin was reported in sheep [2], goat [3,4,5], lactating cow[6] and cross-bred calves[7,8] except in Ongole cattle. Ongole breed of cattle is a world famous triple purpose breed, known for its hardiness, thriftiness and rustling ability [9] is an asset to the marginal farmers in Andhra Pradesh. The present study is designed to investigate the pharmacokinetic properties of pefloxacin in healthy and febrile ongole calves.

EXPERIMETAL SECTION

A total of six healthy Ongole calves of uniform age and weight (80 ± 5 kg) were used. The calves were housed at Livestock Research Station (LRS), Lam, Guntur, Andhra Pradesh, in well ventilated animal sheds. The experimental protocol was approved by Institutional Animal Ethics and Biosafety Committee. Pefloxacin as pefloxacin mesylate dihydrate was supplied by M/s Wockahrdt Ltd., Aurangabad, was used. In the phase 1 of the study, a 10% solution of pefloxacin in sterile distilled water was used for administration. Pharmacokinetic study was performed by injecting pefloxacin into the left gluteal muscle and collecting blood samples (3-4 ml) by jugular venipuncture into unheparinized tubes at before the administration (0) and 2, 5, 10, 15, 30 and 45 min, and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48 h after pefloxacin administration. After phase 1 a wash out period of 14 days was allowed and phase 2 study was performed after inducing the febrile condition by administration of *Escherichia coli* endotoxin

(Lipopolysaccharide LPS, serotype O55: B5,L-2880, SIGMA, USA) as 1% solution in sterile normal saline @ 1 µg/kg body weight intravenously. Fever was induced in 25-45 min and persisted for 8-10 h after injection. A rise of 1-1.5°F rectal temperature was considered as indication of febrile condition. Similar protocol of phase 1 study for drug administration and blood collection was followed for phase 2 study. Sera samples were collected after centrifuging the clotted blood samples at 3000 rpm for 15 min and stored at -20° C until assayed. The concentration of drug in the serum was assayed by the microbiological assay – agar plate diffusion method [10]. *Escherichia coli* ATCC 25922 (MTCC 443 - freeze dried) obtained from Institute of Microbial Technology, Chandigarh, India, was used as organism for assay. Organisms were maintained in nutrient broth (HIMEDA) and for assay procedure, Mueller Hinton Agar (HIMEDIA) was used. The concentration of pefloxacin in the sera samples was determined by substituting the respective mean diameter of zone of inhibition in a standard curve. Analytical recovery (94%) was determined by using two known concentrations. Intra-day assay coefficient of variation (6.4% and 7.9%) was determined by assaying two standard serum samples (0.1 and 1.0 µg ml^{-1}) four times each within 24h. Inter-day assay coefficient of variation (6.1% and 3.9%) was determined by assaying two standard serum samples (0.1 and 1.0 µg ml^{-1}) on four occasions at least 24 h apart. Pharmacokinetic parameters were calculated using an interactive least - squares nonlinear regression programme with personal computer software, "PHARMKIT" [11] and according to the methods described by Gibaldi and Perrier [12]. The duration of pharmacological effect t_d is calculated based on minimum therapeutic concentration (MTC) and β [13].

$$t_d = \frac{2.3}{\beta} \times \log \frac{dose}{MTC}$$

A concentration ranging from 0.1 to 0.2 µg ml^{-1} of serum with an average of 0.1-0.14 µg ml^{-1} was reported to be Minimum Therapeutic Concentration of fluoroquinolones against various species of pathogens [14].

Bioavailability (F) was calculated from the following formula using the intravenous data corresponding to healthy and febrile calves produced in the laboratory.

$$F = \frac{AUC\ extra\ vascular}{AUC\ \ intravenous} \times 100$$

The pharmacokinetic data obtained were analyzed statistically by applying 2-tailed paired t-test.

RESULTS AND DISCUSSION

Following single intramuscular administration of pefloxacin the concentration in the serum was detectable up to 12 h in healthy calves and up to 8 h in febrile calves. The concentration at different time intervals after single intramuscular administration in healthy and febrile ongole calves is presented in Table 1. Following intramusclar administration the serum concentration - time data for pefloxacin was following a one compartment-open model. The pharmacokinetic variables of pefloxacin after single intramuscular injection in healthy and febrile ongole calves are presented in Table 2. After single intramuscular administration, pefloxacin exhibited an absorption half life ($t_{½}$ ka) of 0.45 ± 0.038 h in healthy calves which is significantly ($p<0.05$) lower than that of febrile calves (0.631 ± 0.034 h) and an elimination half - life ($t_{1/2\beta}$') of 1.620 ± 0.037 h which is significantly ($p<0.05$) higher than that of febrile calves (1.020 ± 0.018 h). The $AUC_{(0-\infty)}$ of 24.965 ± 0.036 µg h ml^{-1} and a mean residence time (MRT) of 3.061 ± 0.034 h were recorded in healthy calves when compared to significantly ($p<0.05$) lower values (11.493 ± 0.123 µg.h.ml^{-1} and 2.424 ± 0.023 h respectively) recorded in febrile condition. The peak concentration in serum in healthy calves (c_{max}) of 6.437 ± 0.021 µg ml^{-1} was significantly ($p<0.05$) higher than that of febrile calves (3.550 ± 0.052 µg. ml^{-1}) and there was no significant difference in the time to achieve peak concentration (t_{max}) in both healthy and febrile calves (1.207 ± 0.01h and 1.203 ± 0.022 h, respectively) . The bioavailability (F) of pefloxacin was 85.5% and 83.676% in healthy and febrile calves respectively. The duration of pharmacological effect (t_d) of pefloxacin was 9.958 ± 0.134 h in healthy calves which was significantly higher (6.267 ± 0.109 h) than that of febrile calves.

When pefloxacin was administered to ongole calves as single intramuscular injection, the data exhibited one - compartment open model, which was similar to pefloxacin administration in sheep intramuscularly [2]. Higher bioavailability of pefloxacin (85.52%) achieved indicated complete and rapid absorption, which was evidenced by achievement of C_{max} (6.437 ± 0.021 µg ml^{-1}) in short period (t_{max}, 1.207 ± 0.012 h). The $t_{1/2\beta}$' exhibited by ongole calves was lower than that of sheep [2] and similar to that of lactating goat [5].

Table: 1. Serum concentration of pefloxacin (µg ml^{-1}) at different time intervals after single intramuscular administration (10 mg kg^{-1}) in healthy and febrile Ongole calves

Time (h)	Healthy Calves (Mean ± SE)	Febrile Calves (Mean ± SE)
0.083 (5 min)	0.458 ± 0.005	0.174 ± 0.011
0.166 (10 min)	1.508 ± 0.039	0.810 ± 0.017
0.25 (15 min.)	2.813 ± 0.085	1.330 ± 0.022
0.5 (30 min.)	4.481 ± 0.066	2.425 ± 0.092
0.75 (45 min.)	5.593 ± 0.092	3.087 ± 0.087
1	6.317 ± 0.023	3.721 ± 0.135
1.5	6.949 ± 0.069	3.519 ± 0.097
2	5.799 ± 0.072	3.060 ± 0.057
3	3.640 ± 0.130	1.959 ± 0.034
4	2.657 ± 0.010	1.072 ± 0.031
5	1.747 ± 0.026	0.627 ± 0.021
6	1.065 ± 0.034	0.318 ± 0.018
8	0.591 ± 0.043	0.099 ± 0.010
10	0.242 ± 0.019	-
12	0.094 ± 0.003	-
24	-	-
72	-	-

Table: 2 Pharmacokinetic parameters of pefloxacin in healthy Ongole calves after single intramuscular administration

Parameter	Unit	Healthy Calves (Mean ± SE)	Febrile Calves (Mean ± SE)
Ka	h^{-1}	1.538 ± 0.041^{B}	1.127 ± 0.052^{A}
β'	h^{-1}	0.428 ± 0.039^{A}	0.681 ± 0.012^{B}
$t_{1/2\ Ka}$	h	0.452 ± 0.038^{A}	0.631 ± 0.034^{B}
$t_{1/2\beta'}$	h	1.620 ± 0.037^{B}	1.020 ± 0.018^{A}
AUC	µg h ml^{-1}	24.965 ± 0.036^{B}	11.493 ± 0.128^{A}
MRT	h	3.061 ± 0.034^{B}	2.424 ± 0.023^{A}
Cmax	µg ml^{-1}	6.437 ± 0.021^{B}	3.550 ± 0.052^{A}
Tmax	h	1.207 ± 0.012^{A}	1.203 ± 0.022^{A}
t_d	h	9.958 ± 0.134^{B}	6.267 ± 0.109^{A}

Values with different alphabets as superscripts differ significantly (p<0.05) when analysed by paired sample t-test (2-tailed).
Abbreviations: *Ka- Absorption rate constant; β'- Elimination rate constant; t1/2 Ka- Absorption half-life; t1/2β'- Elimination Half-life; AUC- Area under the curve; MRT- Mean residence time; Cmax- Maximum concentration of the drug; Tmax- Time to achieve maximum concentration; Td- Duration of therapeutic effect*

The higher elimination rate constant ($_\beta$') in febrile calves compared to healthy ongole calves indicated the faster elimination of drug in the febrile condition. The lower value for $t_{1/2\beta}$' in febrile condition supported the quick metabolism or elimination of the drug during fever. The AUC and MRT observed during fever in ongole calves were lower than that observed in healthy ongole calves. This indicates that lesser area was covered by the drug in febrile condition, suggesting quicker elimination. The value of t_d during fever indicated that the therapeutic concentrations were maintained up to 6.267 ± 0.109 h. Hence at the given dose (10 mg kg^{-1}) in febrile ongole calves, to maintain therapeutic concentrations of pefloxacin in serum, pefloxacin should be administered at around eight hour interval.

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