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Effect of Meloxicam on the Phrmacokinetics of Pefloxacin and Its Active Metabolite Norfloxacin in Female Goats

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ABSTRACT

A study on pharmacokinetics of pefloxacin and kinetic interaction between pefloxacin (5 mg/kg) and meloxicam (0.5 mg/kg) was carried out through intravenous route in 5 female goats weighing 18-22 kg. A wash out period of 3 weeks was used before each injection. Blood (0.042-48 h) and urine (0.042-72 h) samples were collected. Estimation of pefloxacin and its active metabolite norfloxacin were carried out by using High Performance Liquid chromatography (HPLC). Shorter distribution half life ($t_{1/2}$ α) of 0.16 h and elimination half life ($t_{1/2}$ β) of 2.42 h were noted in pefloxacin alone administration and non-significant differences were noted in combination with meloxicam. Significantly ($P<0.05$) longer $t_{1/2}$ β was obtained for norfloxacin in combined administration as compared to alone administration of pefloxacin. Significantly ($P<0.05$) lower total body clearance (Cl_B) of 5.92 ml/kg/min was obtained for norfloxacin in combined administration as compared to alone administration (16.62 ml/kg/min). Significantly ($P<0.05$) higher Vd_{area} of 0.98 L/kg was obtained in combined administration as compared to alone administration (Vd_{area} = 0.76 L/kg). This may be the reason that significantly ($P<0.05$) higher approximate tissue to plasma concentration ratio ($T^{\approx}P$) of 8.56 was noted for pefloxaxcin in combined administration as compared to alone administration (3.95). Significantly ($P<0.05$) higher % conversion of pefloxacin to norfloxacin (60.70) was noted in combined administration as compared to alone administration (22.34). Further, the calculated dosage regimen for maintaining minimum therapeutic concentration was found to be significantly ($P<0.05$) lower in combination as compared to alone administration. **Keywords:** - Kinetics, Pefloxacin, Meloxicam, Goats

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INTRODUCTION

Pefloxacin (PEF), a member of fluoroquinolone antimicrobials is transformed into several metabolites in the body but norfloxacin (NORF) is the main pharmacologically active metabolite [1]. Both PEF and NORF are bactericidal at low concentrations for a broad spectrum of gram-negative and gram-positive bacteria as well as mycoplasma [2]. Further, it is also useful in the treatment of serious infections caused by intracellular bacteria [3]. Pharmacokinetics of PEF in man [4, 5, 6], goat [7, 8], cow [9], dog [10], chicken [11], albino rat [12] and mice [10] were conducted.

Meloxicam (MEL) is a novel non-steroidal anti-inflammatory drug (NSAID) of oxicam group with excellent anti-inflammatory, analgesic, antipyretic and anti-exudative actions. It also possesses potent anti-arthritic activity and a reduced potential to induce gastric irritation in man and animals. Meloxicam is used in human and veterinary practice for treating non-descriptive pyrexia, painful conditions due to acute and chronic inflammation, muscular pain, joint pain, rheumatic pain, neuralgia, soft tissue injuries, such as sprain or strain and immobility associated with lameness, arthritis, myositis etc. In man, meloxicam has shown reliable efficacy against rheumatic arthritis, osteoarthritis, ankylosing spondylitis, lumbago (low back pain), scapulohumoral periarthritis and neck-shoulder arm syndrome with low gastrointestinal toxicity [13, 14]. It is used in the treatment of both osteoarthritis and rheumatoid arthritis [15, 16] apart from other inflammatory conditions. MEL is recently approved by FDA for use in treating osteoarthritis. It produces its effects by blocking the synthesis of prostaglandins, prostacycline and thromboxane products preferably by inhibiting cyclo-oxygenase-2 (COX-2), which is the most common mediator of pain, inflammation and pyrexia. MEL has been suggested to be a selective COX-2 inhibitor based on *in vitro* studies. When tested *in vivo* in human beings, its selectivity to inhibit COX-2 compared to COX-1 was about 10-12 fold and there was some inhibition of platelet COX-1 mediated thromboxane production after oral treatment with both 10 [17] and 15 mg/kg [18].

Antimicrobials and NSAIDs are frequently used concomitantly. Pharmacokinetic interactions between them have been described [19, 20, 21, 22, 23, 24, 25, 26]. For judicious use of an antimicrobial and a NSAID, a rational dosage regimen is a pre-requisite for which detailed pharmacokinetics of the drug in the same species and similar climate in which the drug is used to be clinically [27]. Pharmacokinetic studies of antimicrobials and NSAIDs are carried out in healthy animals to obtain detailed pharmacokinetic data. From these data appropriate dosage regimen is derived for effective treatment of the diseases when drugs are administered alone. Now, it is well established

that kinetic parameters of a drug may differ during combination therapy resulting into sharp change in dosage regimen. Since no such study is being undertaken with interaction of PEF with MEL in goat, the present study has been undertaken.

MATERIALS AND METHOD

The study was conducted on five clinically healthy female goats of non-descript breed between 20 to 24 months of age and 18 - 22 kg body weight. The goats were housed in animal shed with concrete floor. The goats were maintained on dry fodder, wheat husk and greens as well as routine grazing for at least 4-5 hours a day. Clean drinking water supplied *ad lib*. The experiment was approved by College animal ethical committee and by Rajendra Agricultural university, Pusa (Samastipur) - 848 125, Bihar, India as Ph.D. project.

Experimental design

PEF was administered in each of five healthy goats by intravenous (i.v.) route. A minimum period of 3 weeks was allowed to elapse before administration of the next injection. After conducting kinetic study of PEF alone, PEF + MEL were administered together in combination by intravenous (i.v.) route to investigate the pharmacokinetic interactions of pefloxacin and its active metabolite with meloxicam in goats.

Drugs used

PEF and MEL were used in the present experiment. PEF (Pelox®) infusion - an injectable commercial preparation containing pefloxacin methane sulfonate dihydrate equivalent to 4 mg/ml of PEF marketed by Wockhardt Limited, Mumbai, India was used. MEL, an injectable commercial preparation marketed under the trade name of Melonex® by Intas Pharmaceutical Limited, Ahmedabad, India was used. Each ml of Melonex contains 5 mg of MEL. Standards of pefloxacin powder and norfloxacin powder were obtained from Division of Pharmacology & Toxicology, Indian Veterinary Research Institute, Izatnagar (Bareilly) - 243122 Uttar Pradesh, India.

Collection of biological Samples and their timings

Blood sample (approx. 5 ml) were collected from the contra lateral jugular vein into heparinised glass centrifuge tubes before and at 0.042, 0.083, 0.167, 0.25, 0.333, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 30, 36 and 48 h after iv administration of the drug given alone and in combination. A washout period of 3 weeks was allowed before next injection. Similarly, the samples of urine were also collected at the above noted times as well as at 72 h after i.v. administration of the drug. For collection of urine, a lubricated Foley's balloon catheter (No. 12)

was introduced into the urinary bladder through the urethra with the aid of a flexible metal probe and kept in position by inflating the balloon by giving 20 to 25 ml of sterile water through a syringe. The plasma was separated after centrifugation (2500 rpm for 10 min.) at room temperature and kept in a refrigerator until it was analyzed, usually within 3 days of collection. The plasma and urine collected prior to administration of the drug were used for preparing drug standards in the respective biological fluid**.**

Estimation of drugs

The High performance Liquid Chromatography (HPLC) equipment used comprised of a HPLC pump (Model 515 – Waters, U.S.A.), a dual wavelength absorbance detector (Model 2487 – Waters, U.S.A.), a rheodyne manual injector and a data module/integrator (Model 746 – Waters, U.S.A.). Chromatographic separations were performed using column 3.9 x 150 mm (µ Bondapak ^{TM} C_{18} - Waters, U.S.A., made in Ireland).

Estimation of pefloxacin and its active metabolite norfloxacin by HPLC method

Estimation of PEF and NORF were done simultaneously in plasma and urine by HPLC method as described [28]. Plasma and urine samples were extracted as per method [29].

Chromatographic conditions

The flow rate was 2 ml/min, the effluent wavelength was monitored at 278 nm, loop size was 200 µl, the chart speed was 0.25 mm/min and the detector sensitivity was 2.000 A.U.F.S. (absorbance under full scale) were adopted for HPLC analysis for PEF and its active metabolite NORF. Chromatogram was done at room temperature. Recovery was around 95 – 98%. Limit of detection was noted to be 0.02 and .05 µg/ml for plasma and urine, respectively.

Reagents

All solvents used were of HPLC grade. All other chemicals and reagents were of analytical grade. Freshly prepared triple distilled water was used. PEF and NORF pure base was obtained from Indian Veterinary Research Institute, Izatnagar, Bareilly-243122 (UP), India for preparing standards.

Mobile phase

The mobile phase comprised of acetonitrile : water (15:85 v/v) containing 2 gm of citric acid and 2 gm of sodium acetate per litter and 0.1% triethylamine (v/v). The pH of mobile phase was 4.8.

Preparation of standards of PEF, NORF and combination in plasma and urine

PEF standards of 4, 2, 1, 0.5, 0.25, 0.1, 0.05, 0.025 and 0.01 µg/ml in plasma and urine were prepared. Blank plasma and urine containing no drug was also prepared. Blank sample

containing no drug was also prepared for both plasma and urine, respectively. Combined standards of PEF and NORF in both plasma and urine containing concentrations as noted above were prepared. Blank sample in plasma and urine were also prepared for both PEF and NORF in urine.

Calculation of kinetic parameters

Kinetic parameters of PEF and PEF + NORF were calculated by 2-compartment open model since log plasma concentrations *versus* time curve followed biphasic pattern as per method [30, 31]. NORF, the active metabolite of PEF showed non linear curve and hence kinetic parameters were calculated by using formulae for non-compartmental model [32].

Statistical analysis

Comparison of data was carried out by using paired 't' test [33].

RESULTS AND DISCUSSION

Figure 1 represents the log plasma and urine concentrations (Mean ± SE) *versus* time curve of PEF, NORF, PEF + NORF when given alone and given together with MEL by i.v. route. Significantly ($p < 0.05$) higher plasma concentations of PEF were noted at 12 and 24 h whereas NORF were noted from 0.042 to 36 h when PEF was given alone and given together with MEL, respectively. Similarly, significantly ($p < 0.05$) higher concnentrations of PEF + NORF together were noted form 4 to 36 h when the drugs were given together as compared to alone administration of pefloxacin. Therapeutic concentration in plasma (C_p ther) of ≥ 0.125 µg/ml was maintained up to 10, 8 and 10 h for PEF, NORF and PEF + NORF when PEF was given alone whereas for a longer period of 12, 24 and > 24 h for PEF, NORF and PEF + NORF when PEF was given in combination with MEL. Significantly ($p < 0.05$) higher urine concentrations of PEF, NORF and PEF+ NORF were reached from 0.042 to 48 h, 0.042 to 12 h and 0.042 to 48 h, respectively, when the drugs were given together as compared to alone administration of PEF. Therapeutic concentration in urine (C_u ther) of ≥ 0.125 µg/ml was maintained from 0.042 to 48 h for PEF, NORF and PEF + NORF together when PEF was given alone as well as when administered with MEL.

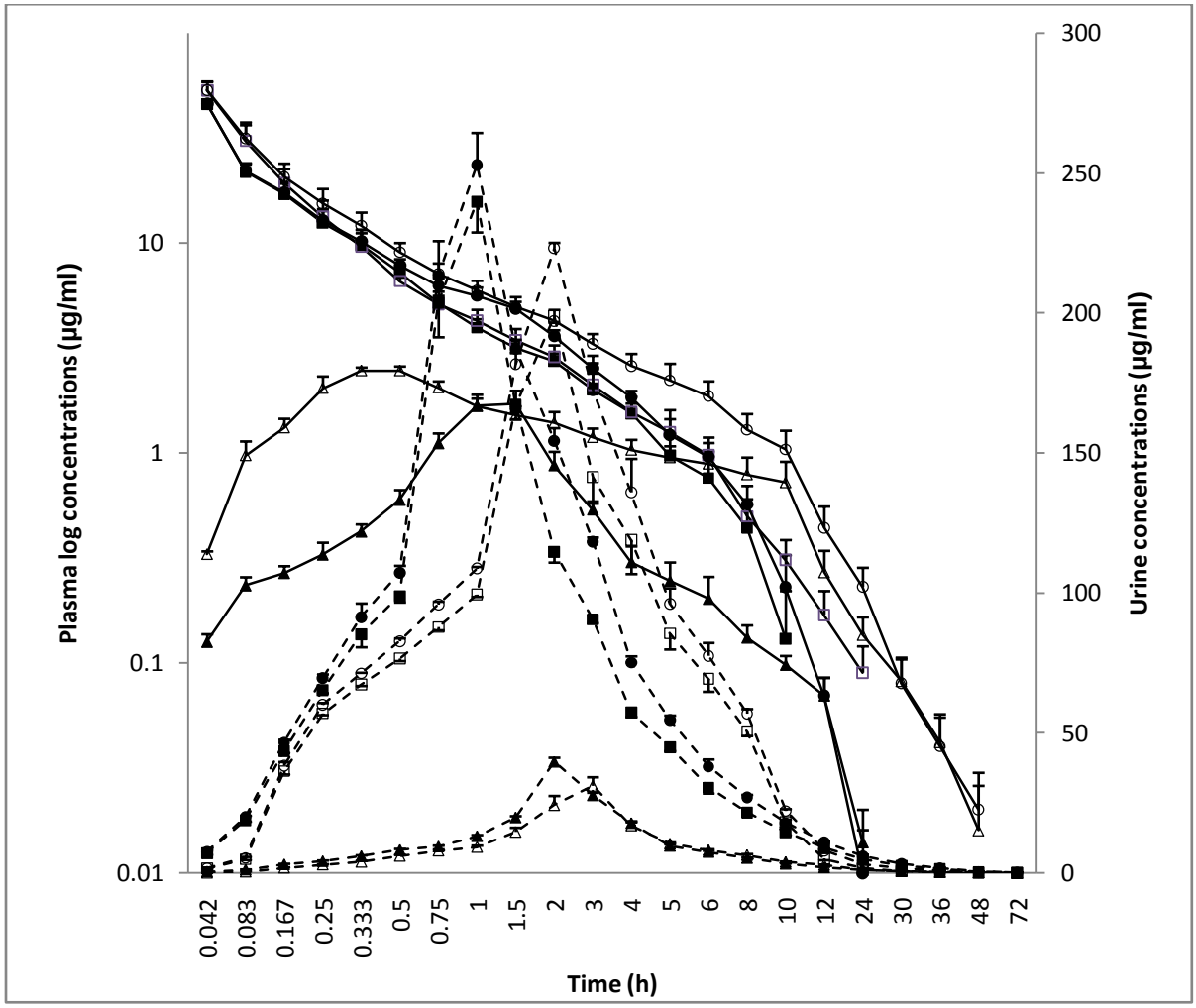

Figure 1: Showing Mean ± S.E.M. log plasma concentrations *versus* time profile of pefloxacin, norfloxacin and both pefloxacin + norfloxacin and urine concentrations of these drugs when pefloxacin was given alone (5 mg/kg, i.v.) and given together with meloxicam following i.v. administration in goats

Legend For Figure

■____■Plasma concentrations of PEF when pefloxacin was given alone
□____□Plasma concentrations of PEF when pefloxacin was given with meloxicam
▲___▲ Plasma concentrations of NORF when pefloxacin was given alone
Δ____ΔPlasma concentrations of NORF when pefloxacin was given with meloxicam
●____●Plasma concentrations of PEF + NORF when pefloxacin was given alone
○____○Plasma concentrations of PEF + NORF when pefloxacin was given with meloxicam
■-----■ Urine concentrations of PEF when pefloxacin was given alone
□-----□ Urine concentrations of PEF when pefloxacin was given with meloxicam
▲----▲ Urine concentrations of NORF when pefloxacin was given alone
Δ-----Δ Urine concentrations of NORF when pefloxacin was given with meloxicam
●-----● Urine concentrations of PEF + NORF when pefloxacin was given alone
○-----○ Urine concentrations of PEF + NORF when pefloxacin was given with meloxicam
⊤ Mean ± S.E.M.

Table 1 and 2 show the comparative kinetic parameters of PEF, NORF and PEF + NORF when PEF was given alone and given together with MEL after a single i.v. administration in goats. Significantly ($P < 0.05$) higher B and Vd_{area} were obtained for PEF when combined with MEL as compared to alone administration. Table 1 show that all kinetic parameters differed significantly for NORF when it was administered along with MEL as compared to alone administration. Significantly ($P < 0.05$) lower β, higher $t_{1/2}$ β and AUC were noted for PEF + NORF when injected along with MEL as compared to alone administration of PEF (Table 2). Table 3 shows priming or loading (D*), maintenance dose (D_0) at four therapeutic levels (C_P^{∞} min) *viz.*, 0.125, 0.25, 0.5 and 1.0 µg/ml at the dosage interval (λ) of 8 and 12 h of PEF in healthy goats. The table reveals that significantly ($P < 0.05$) lower D* and D_0 are required at λ of 8 h at all therapeutic levels when PEF was administered along with MEL as compared to alone administration. Table - 3 also shows that though higher D* and D_0 are calculated at λ of 12 h but they are non-significant.

Table 1: Comparison of kinetic parameters of pefloxacin and norfloxacin when pefloxacin (5 mg/kg) given alone and when given together with meloxicam (0.5 mg/kg) in goats following intravenous administration

Parameter (unit)	Pefloxacin given alone		Pefloxacin + meloxicam combined administration	
	Pefloxacin	Norfloxacin	Pefloxacin	Norfloxacin
A (µg/ml)	28.768 ± 2.703		42.766 ± 3.821^{+}	
B (µg/ml)	4.938 ± 0.464		3.520 ± 0.155*	
C_p^o (µg/ml)	33.706 ± 3.044		46.286 ± 3.883^{+}	
α (h^{-1})	4.585 ± 0.532		6.207 ± 1.923^{+}	
$t_{1/2}$ α (h)	0.160 ± 0.018		0.144 ± 0.030^{+}	
β (h^{-1})	0.291 ± 0.019	0.244 ± 0.024	0.221 ± 0.050^{+}	0.121 ± 0.013*
$t_{1/2}$ β (h)	2.418 ± 0.151	2.956 ± 0.304	3.590 ± 0.812^{+}	5.976 ± 0.607*
AUC (µg/ml.h)	23.596 ± 2.082	5.080 ± 0.283	26.784 ± 3.974^{+}	15.922 ± 2.514*
AUMC (µg/ml.h^2)	61.248 ± 7.191	22.06 ± 3.291	101.83 ± 21.52^{+}	145.92 ± 33.911*
MRT (h)	2.574 ± 0.107	4.268 ± 0.438	3.556 ± 0.460^{+}	8.626 ± 0.875*
K_{12} (h^{-1})	2.504 ± 0.357		4.417 ± 1.955^{+}	
K_{21} (h^{-1})	0.935 ± 0.124		0.691 ± 0.213^{NS}	
Kel (h^{-1})	1.437 ± 0.082		1.986 ± 0.461^{NS}	
Fc	0.203 ± 0.006		0.114 ± 0.008*	
T ≈ P	3.950 ± 0.173		8.560 ± 0.868*	
Vd_{area} (L/kg)	0.758 ± 0.062		0.976 ± 0.043*	
Cl_B (ml/kg/min)	3.668 ± 0.338	16.61 ± 0.949	3.846 ± 1.092^{NS}	5.916 ± 1.092*
% conversion of				

pefloxacin to norfloxacin ($AUC_{PEF}/AUC_{NO\ RF}$) x 100	22.338 ± 2.595	-	60.704 ± 5.258*

^{NS} = Non significant * P<0.05

A = zero time intercept for distribution phase; B = zero time intercept for elimination phase; C_p^0 (µg/mL) = theoretical zero time concentration (A+B); α = distribution rate constant; $t_{1/2}$ α = distribution half life; β = elimination rate constant; $t_{1/2}$ β = elimination half life; AUC = total area under plasma drug concentration curve; AUMC = area under first moment curve; MRT = mean residential time; K_{12} = rate constant of drug transfer from central compartment to peripheral compartment; K_{21} = rate constant of drug transfer from peripheral to central compartment; Kel = rate constant of drug elimination from central compartment; Fc = fraction of drug available for elimination from central compartment; T ≈ P = approximate tissue to plasma concentration ratio; Vd_{area} = apparent volume of distribution; Vd_{SS} = volume distribution at steady state; Cl_B = total body clearance.

Table 2: Comparison of important kinetic parameters of pefloxacin + norfloxacin together calculated by 2-compartment open model when pefloxacin (5 mg/kg) given alone and when given in combination with meloxicam (0.5 mg/kg) in goats following intravenous administration

Parameter (unit)	Pefloxacin given alone	Pefloxacin + meloxicam combined administration
	Pefloxacin + Norfloxacin	Pefloxacin + Norfloxacin
A (µg/ml)	24.886 ± 6.618	22.442 ± 3.896^{+}
B (µg/ml)	5.902 ± 1.372	3.678 ± 0.392^{+}
α (h^{-1})	4.046 ± 1.535	1.771 ± 0.166^{+}
$t_{1/2}$ α (h)	0.296 ± 0.082	0.402 ± 0.033^{+}
β (h^{-1})	0.313 ± 0.046	0.129 ± 0.011*
$t_{1/2}$ β (h)	2.396 ± 0.318	5.492 ± 0.433*
AUC (µg/ml.h)	26.334 ± 2.511	42.784 ± 6.629*
Vd_{area} (L/kg)	0.672 ± 0.094	1.006 ± 0.131^{+}

$^{+}$ Non-significant * P<0.05

Pharmacokinetic interactions between antimicrobials and NSAIDs are well recorded by many workers [19, 20, 21, 22, 23, 24, 25, 26]. Significantly (p < 0.05) higher Vd_{area} of 0.976 ± 0.043 L/kg was obtained for PEF when given along with MEL as compared to the value of 0.758 ± 0.062 L/kg for PEF when administered alone. This may be due to higher distribution of PEF into various organs and tissues when injected along with MEL as compared to its alone administration (Table 1). This statement is further supported by significantly (p <0.05) higher T≈P of 8.560 ± 0.868

when both the drugs were given together as compared to the value of 3.950 ± 0.173 for PEF when administered alone.

The half-lives of most antimicrobials that undergo extensive metabolism are shorter in cattle (and other ruminants) than in monogastric species, particularly human being [34]. The $t_{1/2}$ β of PEF in man was noted to be 11.0 h [35] and in sheep as 6.88 h [36] post i.v. administration whereas it was 2.63 in buffalo calf [37], 2.53 h in cow [9], 2.21 h in crossbred calf [38] and 3.39 h [39], 3.53 h [7]& 1.12 h [8]in goat. The above data show that in ruminants including goat, the $t_{1/2}$ β is shorter for PEF and intra species variation is also noted. Baggot [34] stated that inter and intra species variations are noted in the half-lives of individual drugs in antimicrobial class. The data of the present study confirms the above statement.

In the present study, Vd_{area} of 0.758 ± 0.062 L/kg was obtained for PEF when administered alone. Vd_{area} of 1.94 L/kg in man after oral administration [10], 4.62 L/kg in buffalo calf [37], 0.68 L/kg in cow [9], 1.44 L/kg in crossbred calf [38] and 1.59 L/kg [7], 1.08 L/kg [8] & 5.14 L/kg [40] post i.v. administrations in goat were recorded. The above data show that PEF is expected to be distributed well in different body fluids and tissues in man and animals. Further, higher value of Vd_{area} may denote higher metabolism/excretion or both [34]. This is supported that PEF undergoes conversion to NORF and it was 22.338 ± 2.595% in the present study. When given in combination with MEL, there is a significant ($p < 0.05$) conversion of pefloxacin to 60.704 ± 5.258% as NORF. Significantly ($p < 0.05$) higher Vd_{area} of 0.976 ± 0.043 L/kg was recorded when PEF was given in combination with MEL as compared to its alone administration. Accordingly, significantly ($p < 0.05$) higher concentrations of PEF in urine were noted at most of the time intervals when PEF was administered with MEL as compared to its alone administration (Figure 1).

Baggot [34] stated that the clinical effectiveness of aminoglycosides and fluoroquinolones is influenced both by the height of the peak plasma concentration relative to MIC (Cmax : AUC) and the area of plasma concentration-time curve that is above the MIC during the dosage interval (AUIC = AUC/MIC). The former is relatively more important for fluoroquinolones. Maximum activity is achieved when Cmax is in the range 5-10 times MIC. MIC of PEF is considered to be in the range of 0.125 to 1µg/ml for majority of bacteria [7, 38]. Cmax of 45.95 ± 2.164 µg/ml was obtained for PEF at 0.042 h while Cmax of 1.714 ± 0.265 µg/ml was attained for NORF at 1.5 h when PEF was given alone. This is quite higher than 10 times of MIC even 1µg/ml is considered as MIC for PEF. When PEF was given along with MEL a higher Cmax value of 53.41 ± 5.052

µg/ml was achieved for PEF at 0.042 h while higher Cmax value of 2.468 ± 0.085 µg/ml was noted for NORF (Figure 1). Cmax: MIC value was calculated to be around 46 and 53, respectively, for PEF when administered alone and when given along with MEL (Figure 1). Similarly, though higher AUIC was calculated for PEF + NORF together when given alone, but significantly ($p < 0.05$) higher value can be calculated for PEF + NORF together with meloxicam since significantly ($p < 0.05$) higher AUC was noted (Table 2).

Baggot [34] stated that though aminoglycosides and fluoroquinolones induce a post antibiotic sub MIC effect (PASME) on some species of gram-negative bacteria, because of its variable duration, generally 1-6 h, the post antibiotic effect is not taken into account when calculating dosage regimen. Comparison of calculated dosage regimen of pefloxacin given alone and given together with meloxicam reveals that γ of 8 h, the calculated D* and D_0 for maintaining MIC (C_p min) at 0.125, 0.25, 0.5, 1 µg/ml are calculated to be significantly ($p < 0.05$) lower when pefloxacin was given together with meloxicam as compared to its alone administration (Table 3). Though at γ of 12 h lower D* and D_0 are noted when pefloxacin was administered together with meloxicam as compared to its alone administration but the data are noted to be non-significant.

Table 3: Comparison of calculated dosage regimens of pefloxacin when given alone and when given together with meloxicam in goats following intravenous administration

C_p^{∞} min (µg/ml)	γ (h)	Dose (mg/kg)	Pefloxacin given alone	Pefloxacin + Meloxicam given together
0.125	8	D*	1.128 ± 0.290	0.376 ± 0.087*
		D_0	1.044 ± 0.295	0.248 ± 0.071*
	12	D*	4.962 ± 1.962	0.654 ± 0.184^{+}
		D_0	4.880 ± 1.971	0.530 ± 0.168^{+}
0.25	8	D*	2.252 ± 0.578	0.750 ± 0.172*
		D_0	2.086 ± 0.592	0.498 ± 0.139*
	12	D*	9.928 ± 3.925	1.314 ± 0.368^{+}
		D_0	9.760 ± 3.941	1.058 ± 0.336^{+}
0.50	8	D*	4.504 ± 1.157	1.498 ± 0.344*
		D_0	4.168 ± 1.182	0.998 ± 0.279*
	12	D*	19.854 ± 7.851	2.622 ± 0.737^{+}
		D_0	19.518 ± 7.883	2.120 ± 0.672^{+}
1	8	D*	9.010 ± 2.314	2.998 ± 0.688*
		D_0	8.338 ± 2.365	1.992 ± 0.559*
	12	D*	39.710 ± 15.702	5.244 ± 1.473^{+}
		D_0	39.038 ± 15.766	4.238 ± 1.344^{+}

+ = Non-significant, * = P<0.05 , D*= Priming or Loading dose

Do = Maintenance dose, γ = Dosage interval

C_p^{∞} min = Minimum therapeutic concentration in plasma (MIC)

CONCLUSION

The study revealed that pefloxacin and meloxicam can be given together since there is a beneficial interaction and a significant reduction in the dosages of pefloxacin. Thus, the study establishes clearly that pefloxacin and meloxicam can be used successfully for treating systemic, urinary tract and other infections including synovitis and other inflammatory diseases of joint and bone.

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REFERENCES

1. Montay G, Blain Y, Roquet F, LeHir A. High performance liquid chromatography of pefloxacin and its main active metabolites in biological fluids. J Chromatogr 1983; 272: 359 – 65.
2. Hooper DC, Wolfson JS. Fluoroquinolone antimicrobial agents. New Eng J Med 1991; 7: 384 – 94.
3. Leysen DC, Haemers A, Pattyn SR. Mycobacteria and the new quinolones. Antimicrob Agents Chemother 1989; 33**:** 1-5.
4. Danan G, Montay G, Cunci R, Erlinger S. Pefloxacin kinetics in cirrhosis. Clin Pharmacol Ther 1985; 38: 439 – 42.
5. Cardey J, Silvain C, Bougquet S, Breux JP, Becq-Giraudan B, Fourtillan JP, Beauchant M. Oral pharmacokinetics and ascitic fluid penetration of pefloxacin in cirrhosis. Eur J Clin Pharmacol 1987; 33**:** 469 – 72.
6. Sharma AK, Khosla R, Kela AK, Mehta VL. Fluoroquinolones: Antimicrobial agents of the 90's. Ind J Pharmacol 1994; 26: 249 – 61.
7. Ansari MK, Sinha SP, Jayachandran C, Singh MK. Pharmacokinetics and distribution of pefloxacin in biological fluids of lactating goats after intravenous administration. Ind J Anim Res 2000; 34: 95 – 99.
8. Malik JK, Rao GS, Ramesh S, Muruganandan S, Tripathi HC, Shukla DC. Pharmacokinetics of pefloxacin in goats after intravenous or oral administration. Vet Res

Commun 2002; 26: 141 – 49.

9. Patil RV, Gatne MM, Somkumar AP, Ranade VV. Pharmacokinetics and milk concentration of pefloxacin injection (Pelwin) in lactating cows. Ind Vet J 1996; 73: 1130 – 2.
10. Montay G, Goueffon Y, Roquet F. Absorption distribution metabolic fate, and elimination of pefloxacin mesylate in mice, rats, dogs, monkeys and humans. Antimicrob Agents Chemother 1984; 25: 463 – 72.
11. Chousalkar MS. Pharmacokinetic studies of pefloxacin and its residue studies in tissues and eggs of chicken. MVSc thesis submitted to Konkan Krishi Vidyapeeth, Dapoli, Maharashtra, India; 1995.
12. Cochereau-Massin I, Bouchet J, Faurisson F, Vallois JM, Lacombe P, Pocidalo JJ. Ocular kinetics of pefloxacin after intramuscular administration in a albino and pigmented rabbits. Antimicrob Agents Chemother 1991; 35: 1112 – 5.
13. Fleischmann R, Iqbal I, Slobodin G. Meloxicam. Expert Opin Pharmacother 2002; 3: 1501 – 12.
14. Ogino K, Saita K, Osugi T, Satoh H. Meloxicam (Mobic): a review of its pharmacological and clinical profile. Nippon Yakurigaku Zasshi 2002; 120: 391 – 7.
15. Engelhardt G, Bogel R, Schnitzler CHR, Utzmann R. Meloxicam: Influence on arachidonic acid metabolism I *In vitro* findings. Biochem Pharmacol 1996 a; 51: 21 – 8.
16. Engelhardt G, Bogel R, Schnitzler CHR, Utzmann R. Meloxicam influence on arachidonic acid metabolism. II. *In vivo* findings. Biochem Pharmacol 1996 b; 51: 29 – 38.
17. Busch U, Schmid J, Heinzel G, Schmaus H, Baier LJ, Huber C, Roth W. Pharmacokinetics of meloxicam in animals and the relevance to humans. Drug Metabol Dispos 1998; 26 : 576 – 83.
18. Panara MR, Renda G, Sciulli MG, Santini G, Di-Giamberardino MD, Rotondo MT, Tacconelli S, Seta F, Patrono C, Patrignani P. Dose-dependent inhibition of platelet cyclooxygenase-1 and monocyte cyclooxygenase-2 by meloxicam in healthy subjects. J Pharmacol Exp Ther 1999; 290: 276 – 80.
19. Mueller EA, Kovarik JM, Koelle EU, Merdjan H, Johnston A, Hitzenberger G. Pharmacokinetics of cyclosporine and multiple – dose diclofenac during co-administration. J Clin Pharmacol 1993; 33: 936 – 43.

20. Nergelius G, Vinge E, Bengtsson HI, Bjorkman R, Grubb A. No effect of diclofenac on the pharmacokinetics of cloxacillin. Pharmacol Toxicol 1997; 81: 26 – 30.
21. Tang W, Stearns RA, Kwei GY, Iliff SA, Miller RR, Egan MA, Yu NX, Dean DC, Kumar S, Shou M, Lin JH, Baillie TA. Interaction of diclofenac and quinidine in monkeys: stimulation of diclofenac metabolism. J Pharmacol Exp Ther 1999; 291: 1068 – 74.
22. Nitesh Kumar, Singh SD, Jayachandran C. Pharmacokinetics of enrofloxacin and its active metabolite ciprofloxacin and its interaction with diclofenac after intravenous administration in buffalo calves. Vet J 2003; 165: 302 – 06.
23. Kumarasamy P, Nitesh Kumar, Sahni YP. Effect of levofloxacin on the pharmacokinetics of nimesulide in lactating goats. J Vet Pharmacol Toxicol 2009; 8: 26-9.
24. Sadariya KA, Gothi AK, Patel SD, Patel HV, Bhavsar SK, Thaker AM. Pharmacokinetic interaction of moxifloxacin and meloxicam following intramuscular administration in rats. Pharma Science Monitor 2010; 1(1): 27-34.
25. Tohamy MA. Pharmacokinetics interactions of flunixin and orbifloxacin in buffalo calves. Insight Pharmaceutical Sciences 2011; 1(3): 29-33.
26. Abo-EL-Sooud KL, AL-Anati. Pharmacokinetic study of flunixin and its interaction with enrofloxacin after intramuscular administration in calves. Vet World 2011; 4(10): 449-454.
27. Nawaz M, Khan H, Rahman Z. Pharmacokinetics of sulfadimidine in ruminants. Proceedings of the First International Congress of Veterinary Pharmacology, Cambridge, UK; 1980: 57 – 63.
28. Montay G, Tassel JP. Improved HPLC determination of pefloxacin and its metabolite norfloxacin in human plasma and tissue. J Chromatogr 1985; 339: 214 – 18.
29. Nielsen P, Hansen NG. Bioavailability of enrofloxacin after oral administration to fed and fasted pigs. Pharmacol Toxicol 1997; 80: 246 – 50.
30. Baggot JD. Principles of drug distribution in domestic animals. In: The basis of veterinary clinical pharmacology, 1st ed., Philadelphia, London, Toranto: WB Saunders Company; 1977.
31. Gibaldi M, Perrier D. Pharmacokinetics. Vol. II. New York: Marcell Dekker Inc; 1985.
32. Singh B. Non-compartmental pharmacokinetic analysis of plasma level data through statistical moments approach: a worksheet instance. ICAR short course on "Recent Approaches in Clinical Pharmacokinetics and Therapeutic Monitoring of Drugs in Farm Animals". Oct 25 – Nov 3. Division of Pharmacology and Toxicology. Indian Veterinary

Research Institute, Izatnagar, Uttar Pradesh, India; 1999: 36 – 40.

33. Snedecor GW, Cochran WG. Statistical Methods. 6th ed., New Delhi, India: Oxford and IBH Publishing Company; 1967.
34. Baggot JD. The physiological basis of veterinary clinical pharmacology. Osney Mead, Oxford, London, UK: Blackwell Science Ltd; 2001.
35. Frydman, AM, Le Roux Y, Lefebvre MA, Djebbar F, Fourtillan JB, Gaillot J. Pharmacokinetics of pefloxacin after repeated intravenous and oral administration (400 mg bid) in young healthy volunteers. J Antimicrob Chemother 1986; 17: 65 – 79.
36. Moutafchieva R, Diouvinov D. Pharmacokinetics of pefloxacin in sheep. J Vet Pharmacol Ther 1997; 20: 405 – 7.
37. Prakash N. Pharmacokinetics of pefloxacin after single intravenous administration in buffalo calves. Ind Vet J 2003; 80: 746 – 8.
38. Srivastava AK, Dumka VK, Deol SS. Disposition kinetics and urinary excretion of pefloxacin after intravenous injection in crossbred calves. Vet Res Commun 2000; 24: 189 – 96.
39. Roy BK, Pandey SN, Sinha KP, Thakur DK, Singh KK. Pharmacokinetics of pefloxacin in goats. Ind J Pharmacol 1997; 29: 435 – 6.
40. Abd El-Aty AM, Goudah A. Some pharmacokinetic parameters of pefloxacin in lactating goats. Vet Res Commun 2002; 26: 553 – 61.