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PK-PD of marbofloxacin along with meloxicam after single intramuscular administration in buffalo calves

Dinesh MB, SK Sharma, JS Lamba, MM Lonare and Dr. SK Singh

Abstract
Marbofloxacin is a third generation broad spectrum fluoroquinolone developed exclusively for use in veterinary medicine against many pathogens of veterinary importance. NSAIDs are the most commonly used group of drugs prescribed by physician along with antibiotics. The present study was carried out to investigate the effect of meloxicam administration on the disposition of marbofloxacin at single dose i.e 8 $mg.kg^{-1}$ in 6 months - 1 year old buffalo calves. Meloxicam (0.5 $mg.kg^{-1}$) was administered intramuscularly followed by marbofloxacin at 8 $mg.kg^{-1}$ i.m to the buffalo calves. The concentration of marbofloxacin in plasma was estimated using HPLC. The plasma concentration was maintained upto 12 h. Vd_{area} of marbofloxacin was found to be 8.7 ± 1.50 $L.kg^{-1}$ indicating good tissue distribution. The values of C_{max}, t_{max} $AUC_{0-\infty}$ and AUMC found to be 1.19 ± 0.07 $\mu g.ml^{-1}$, 1.00 h, 6.11 ± 0.60 $\mu g.ml^{-1}.h$ and 29.26 ± 2.73 $\mu g.ml^{-1}.h^2$ respectively. The $t_{1/2\beta}$, Cl_B and MRT found to be 4.37 ± 0.28 h, 1.34 ± 0.12 $L.kg^{-1}.h^{-1}$ and 4.64 ± 0.2 h respectively. The selected dose of marbofloxacin (8 $mg.kg^{-1}$) administered i.m, along with meloxicam (0.5 $mg.kg^{-1}$) in buffalo calves was found effective against MIC value ≤ 0.073 $\mu g.ml^{-1}$. Meloxicam seems to affect the pharmacokinetic behavior of marbofloxacin remarkably.

Keywords: PK-PD, marbofloxacin, meloxicam, buffalo calves

Introduction
Antimicrobials are used extensively in both human and veterinary medicine to cure infections. Therefore, it is pertinent to know the antibacterial's spectrum of action, individual host response, interaction with other drugs, antibacterial resistance etc. Fluoroquinolones are a class of compounds in which the bactericidal action is concentration dependant and have a wide spectrum of bactericidal activity, a large volume of distribution and relatively low minimal inhibitory concentrations (MICs) against target micro-organisms (Spreng *et al* 1995; Brown 1996) [1, 2]. Marbofloxacin is a third generation fluoroquinolone antimicrobial drug which has been developed exclusively for use in veterinary medicine (Elzoghby and Aboubakr 2015) [3]. It is a broad spectrum bactericidal and a very potent antibiotic active against many pathogens of veterinary importance, including most gram-negative organisms and some gram-positive bacteria, as well as mycoplasma (Dalhoff 1999) [4]. Non steroidal anti-inflammatory drugs are often used and commonly prescribed in humans and animals for reduction in pain, fever and inflammation in rheumatic problems (Smith *et al* 2008) [5]. Meloxicam, a novel NSAID of the oxicam class is widely recognized as being one of the first commercially available selective cyclooxygenase-2 inhibtor (Ogino *et al* 1997) [6]. In young and adult cattle, meloxicam demonstrated a high oral bioavailability and long elimination half-life, providing an effective and long-lasting analgesia (Coetzee *et al* 2015) [7]. Administration of analgesic, anti-inflammatory drugs, antipyretics along with antibacterials to treat fever and pain is a common practice in veterinary medicine. The buffalo species are more susceptible to pneumonia, pasteurellosis and other bacterial infections, which require treatment with antimicrobial drugs alone and in combination with NSAIDs. Pharmacokinetics of an antibacterial drug may change when administered along with anti-inflammatory drug in animals as reported for tolfenamic acid and marbofloxacin in goats (Sidhu *et al* 2006) [8], levofloxacin with paracetamol and meloxicam in crossbred calves (Dumka 2007) [9] and enrofloxacin with diclofenac in calves and sheep (Ahmed *et al* 2005; Rahal *et al* 2008) [10, 11]. Pharmacokinetic studies today play an important role in drug development and drug evaluation (Derendorf and Meibohm 1999) [12]. Pharmacokinetic parameters are most useful for optimizing the dosage regimen of a drug for different species. Data pertaining to clinical use of marbofloxacin interacting with NSAIDs in buffalo are scarce. Considering the facts present study was aimed to clear the future of marbofloxacin on concomitant administration of meloxicam for the treatment of bacterial

diseases accompanied by inflammation, pain and fever in buffalo species.

Materials and Methods

Experimental animals

The experiment was conducted in four healthy male buffalo calves of 6 to 12 month age weighing around 120-135 kg. Prior to the commencement of experiment, it was ensured that animals have no history of antibacterial and/or NSAIDs treatment. They were housed in a ventilated barn with other buffalo calves at animal house of Department of Pharmacology and Toxicology, GADVASU, Ludhiana. The study was approved by the Institutional Animal Ethics Committee (Order No. VMC/14/1046-73 dated 7.04.2013). The animals were kept under close observation and acclimatized prior to commencement of the experiment and provided with seasonal green fodder and water *ad libitum*.

Drug administration

Meloxicam was administered intramuscularly to the four buffalo calves at the dose rate of 0.5 mg.kg^{-1} followed by marbofloxacin at the dose rate of 8 mg.kg^{-1} body weight.

Collection of blood samples

Blood samples (3-4 ml) were collected from jugular vein of buffalo calves in heparinized vials at specific time intervals of 2.5, 5, 10, 15, 30, 45 min and 1, 2, 4, 6, 8, 10, 12, 24, 36 hrs after the administration of marbofloxacin. Blood samples were centrifuged within 20 minutes at 3000 rpm at 5 ^{o}C for 10 minutes. Plasma was separated and stored at -20 ^{0}C for analysis.

HPLC assay

Marbofloxacin concentration in serum samples was analyzed by reverse-phase high-performance liquid chromatography (HPLC) after extraction as per the method already established with slight modifications. The chromatography was performed with an analytical C18 column (Merck Purospher, particle size 5µ, 250×4.6 mm). The mobile phase consisted of buffer 70% and methanol 30 %. Buffer comprised of 4.0 g di-ammonium hydrogen orthophosphate and 4.0 g tetrabutylammonium hydrogen sulfate dissolved in 800ml HPLC grade water, pH adjusted to 2.7 with orthophosphoric acid. The mobile phase was filtered through a 0.45 µm nylon filter (Millipore, Bedford, MA) under vacuum and sonicated for 30 min. The flow rate was 0.8 ml/min. The detection was performed by UV detection at a wavelength of 295 nm at an ambient temperature of 30 ± 2 ^{0}C. The retention time of marbofloxacin in spiked plasma was 10.27 min with the total run time of 15 min. The TotalChrom software® (version 6.1) was used for instrument control and data analysis.

Serum samples were deproteinized by diluting 600 µl of acetonitrile to 400 µl of thawed plasma samples and the solution was vortexed for 1 min. After centrifugation at 2000 rpm for 15 min at 4 ^{0}C, 250 µl of the supernatant layer was removed and evaporated at 60 ^{0}C to dryness under concentrator plus**.** The residue was reconstituted in a volume of 500 µl buffer and vortexed. The final solution was filtered by syringe filter (0.45µ, nylon filter) and was pipetted into a clean dry autosampler vial. A 50 µl aliquot of the reconstituted sample was injected into the HPLC system. The calibration curve of standard marbofloxacin was prepared by adding the known amount to blank plasma in the range of 0.1 to 10 µg/ml. The regressıon formula was derived from the standard curve and had an R^2 value 0.9998. the limit of quantification and limit of detection values were 0.1 and 0.01, respectively. The recovery of the mentioned method was consistent and efficient (95.69±0.71%). Various pharmacokinetic determinants were calculated from the plasma concentration-time profile of marbofloxacin for each animal by PK solution software (PK Solution Software, version 2.0, USA).

Results and Discussion

To evaluate the disposition of marbofloxacin under the influence of a NSAID drug, meloxicam was administered intramuscularly at the rate of 0.5 mg.kg^{-1} body weight followed by marbofloxacin at the dose rate of 8 mg.kg^{-1} body weight in buffalo calves. Plasma concentration of marbofloxacin when co-administered with meloxicam at different time intervals are mentioned in table 1. The semi-logarithmic graphical representation of mean plasma drug concentration-time profile of marbofloxacin co-administered with meloxicam is mentioned in figure 1.

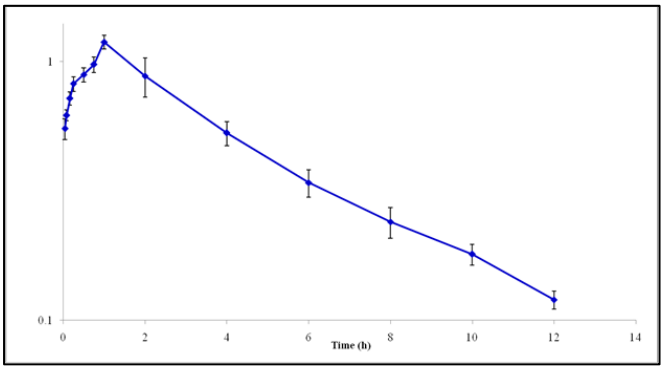

Fig 1: Semi-logarithmic graphical representation of mean plasma concentration of marbofloxacin along with meloxicam in buffalo calves

Table 1: Plasma concentration (µg.ml^{-1}) of marbofloxacin following its intramuscular injection co-administered with meloxicam in buffalo calves

Time (hr)	Animal				Mean ± SE
	A	B	C	D	
0.04	0.59	0.56	0.42	0.66	0.55 ± 0.05
0.08	0.65	0.58	0.58	0.7	0.62 ± 0.03
0.16	0.81	0.66	0.65	0.79	0.72 ± 0.04
0.25	0.92	0.67	0.82	0.86	0.82 ± 0.05
0.5	0.96	0.72	0.95	0.93	0.89 ± 0.05
0.75	1.08	0.78	0.98	1.06	0.97 ± 0.06
1	1.32	0.99	1.28	1.18	1.19 ± 0.07
2	1.02	0.46	1.16	0.89	0.88 ± 0.15
4	0.54	0.37	0.58	0.63	0.53 ± 0.05
6	0.43	0.23	0.36	0.34	0.34 ± 0.04
8	0.23	0.19	0.34	0.23	0.24 ± 0.03
10	0.19	0.15	0.23	0.18	0.18 ± 0.01
12	0.13	0.1	0.14	0.14	0.12 ± 0.009

In the present study, when marbofloxacin was given along with meloxicam, the plasma concentration versus time plot curve was on semi-logarithmic graph tends to fit the two compartment open model. The value of C_{max} and t_{max} were 1.19 ± 0.07 µg.ml^{-1} and 1.00 h, respectively. Similar findings were reported when ketoprofen was administered along with marbofloxacin at 2 mg.kg^{-1} body weight in buffalo calves, where C_{max} and t_{max} values were 0.81µg.ml^{-1} and 0.75 h, respectively (Baroni *et al* 2010) [13]. The values of C_{max} and

t_{max} were 0.82 µg.ml^{-1} and 0.64 h, respectively in buffalo calves when flunixin was administered with marbofloxacin (Baroni *et al* 2011) [14] and 1.201 µg.ml^{-1} and 0.45 h, respectively in goats when marbofloxacin was administered with tolfenamic acid (Sidhu *et al* 2010) [15]. On comparing the present data with that reported by Baroni *et al* (2010) [13] it was found that C_{max} and t_{max} were not significantly altered when marbofloxacin was administered along with meloxicam.

Table 2: Pharmacokinetics of marbofloxacin following in single intramuscular injection co-administered with meloxicam in buffalo calves

Parameter [a]	Unit	Animal				Mean ± SE
		A	B	C	D	
β	h^{-1}	0.19	0.14	0.16	0.15	0.16 ± 0.01
B	µg.ml^{-1}	1.40	0.64	1.30	0.89	1.06 ± 0.18
$t_{1/2\beta}$	H	3.60	4.95	4.30	4.62	4.37 ± 0.28
α	h^{-1}	0.11	0.10	0.13	0.09	0.11 ± 0.008
A	µg.ml^{-1}	0.45	0.44	0.53	0.57	0.50 ± 0.003
$t_{1/2\alpha}$	h	6.30	6.93	5.33	7.77	6.58 ± 0.52
Ka	h^{-1}	7.35	4.99	4.27	7.32	5.98 ± 0.80
A'	µg.ml^{-1}	0.11	0.13	0.06	0.08	0.09 ± 0.02
$t_{1/2\ ka}$	h	0.09	0.13	0.16	0.09	0.12 ± 0.01
C_{max}	µg.ml^{-1}	1.32	0.99	1.28	1.18	1.19 ± 0.07
t_{max}	h	1.00	1.00	1.00	1.00	1.00 ± 0.00
CP^0	µg.ml^{-1}	1.96	1.21	1.89	1.54	1.65± 0.17
AUC	µg.ml^{-1}.h	6.75	4.42	7.16	6.12	6.11 ± 0.60
AUMC	µg.ml^{-1}.h^2	31.50	21.86	34.74	28.94	29.26 ± 2.73
Vd_{area}	L.kg^{-1}	6.23	12.9	6.97	8.70	8.7 ± 1.50
Vd_B	L.kg^{-1}	5.71	12.5	6.15	8.98	8.33 ± 1.57
K_{el}	h^{-1}	0.29	0.27	0.26	0.25	0.26 ± 0.008
$t_{1/2\ kel}$	h	2.38	2.56	2.66	2.77	2.59 ± 0.08
Cl_B	L.kg^{-1}.h^{-1}	1.18	1.80	1.11	1.30	1.34 ± 0.12
MRT	h	4.06	4.94	4.84	4.72	4.64 ± 0.2

Pharmacokinetic parameters of marbofloxacin co-administered with meloxicam in buffalo calves are mentioned in table 2. When marbofloxacin was administered alone at 2 mg.kg^{-1} body weight the Vd_{area} obtained was 1.57 L.kg^{-1} in buffalo calves (Baroni *et al* 2010) [13], 1.24 L.kg^{-1} in calves (AliAbadi and Lees 2002) [16], 0.42 ± 0.06 L.kg^{-1} in calves (Ismail and El-Kattan 2007) [17], 1.5 L.kg^{-1} (Sidhu *et al* 2010) [13] and 0.74 ± 0.068 L.kg^{-1} (Waxman *et al* 2001) [19] in goats. However, when marbofloxacin was administered at 2 mg.kg^{-1} body weight along with ketoprofen, the Vd_{area} of marbofloxacin with was 1.80 L.kg^{-1} in buffalo calves (Baroni *et al* 2010) [13], 2.18 L.kg^{-1} with flunixin meglumine in buffalo calves (Baroni *et al* 2011) [14] and 1.48 L.kg^{-1} with tolfenamic acid in goats (Sidhu *et al* 2010) [15].

The Vd_{area} of marbofloxacin in the present investigation at 8 mg.kg^{-1} body weight along with meloxicam was calculated to be 8.7 ± 1.50 L.kg^{-1}, which is significantly higher from the values discussed above. However, quite similar value for Vd_{area} (7.24 ± 0.645 L.kg^{-1}) was observed for long acting moxifloxacin at 7.5 mg.kg^{-1} body weight when given along with meloxicam in goats (Anjana *et al* 2017) [18]. These values indicate that the Vd_{area} is directly dependant on the administered dose. A high dose of marbofloxacin (8 mg.kg^{-1} body weight) and its high lipophilicity could probably be the reason for high Vd_{area} value in the present study.

In the present study, the $t_{1/2\beta}$ obtained was 4.37 ± 0.28 h, which was significantly lower as compared to the 6.60 h in buffalo calves (Baroni *et al* 2010) [13]. This indicates that significant changes occured regarding the elimination half life when meloxicam was administered with marbofloxacin in buffalo calves. The possible hypothesis for this could either be increased hepatic and renal metabolism, and/or meloxicam decreasing the entero-hepatic recycling of marbofloxacin, and/or meloxicam and marbofloxacin competing for the metabolism through CYP isoforms and/or due to high protein binding capability of meloxicam than marbofloxacin in calves. However, further investigations are required to explain this phenomena.

Clearance of marbofloxacin when given alone at 2 mg.kg^{-1} body weight was found to be 0.168 L.h^{-1}.kg^{-1} in buffalo calves (Baroni *et al* 2010) [13], 0.21 L.h^{-1}.kg^{-1} in calves (AliAbadi and Lees 2002) [16], 3.0 ± 0.36 ml.min^{-1}.kg^{-1} in calves (Ismail and El-Kattan 2007) [17], 0.23 L.h^{-1}.kg^{-1} in goats (Waxman *et al* 2001) [19] and 0.357 L.h^{-1}.kg^{-1} in goats (Sidhu *et al* 2010) [15].

The clearance value obtained in the present study with meloxicam was 1.34 ± 0.115 L.h^{-1}.kg^{-1}, which is high compared to the marbofloxacin alone values at 2 mg.kg^{-1} body weight. The values of clearance reported for marbofloxacin with ketoprofen were 0.173 L.h^{-1}.kg^{-1} in buffalo calves (Baroni *et al* 2010) [13], 0.168 L.h^{-1}.kg^{-1} with flunixin meglumine in buffalo calves (Baroni *et al* 2011) [41] and 0.354 L.h^{-1}.kg^{-1} with tolfenamic acid in goats (Sidhu *et al* 2010). In tune with the present findings, Anjana *et al* (2017) [18] also reported that meloxicam decreases the $t_{1/2\beta}$ and increased the clearance of moxifloxacin in goats.

The data of the present study shows that at 8 mg.kg^{-1} body weight, there was a significant increase in clearance value of marbofloxacin when given along with meloxicam. This can be correlated with decreased elimination half life of marbofloxacin with meloxicam in buffalo calves. The individual factors that can influence clearance are the intrinsic functions of liver or kidneys. In addition, blood flow and the plasma concentration of the drug to the organs of elimination can also affect clearance. In the present experiment, it seems that meloxicam is likely to alter the clearance of the drug marbofloxacin significantly in buffalo calves.

$AUC_{0-\infty}$ of marbofloxacin when administered at 2 mg.kg^{-1} body weight has been reported as 12.44 µg.h.ml^{-1} in buffalo calves (Baroni *et al* 2010) [13], 10.11 µg.h.ml^{-1} in calves (AliAbadi and Lees 2002) [16], 12 ± 1.58 µg.h.ml^{-1} in calves (Ismail and El-Kattan 2007) [17], 8.44 ± 1.42 µg.h.ml^{-1} in goats (Waxman *et al* 2001) [19] and 5.598 µg.h.ml^{-1} in goats (Sidhu *et al* 2010) [15].

In the present study $AUC_{0-\infty}$ was found to be 6.11 ± 0.60 µg.h.ml^{-1} when marbofloxacin was given along with meloxicam in buffalo calves. With respect to the present findings, some workers have reported $AUC_{0-\infty}$ of marbofloxacin to be 11.65 µg.h.ml^{-1} with ketoprofen in buffalo calves (Baroni *et al* 2010) [13], 12.11 µg.h.ml^{-1} with flunixin meglumine in buffalo calves (Baroni *et al* 2011) [14] and 5.655 µg.h.ml^{-1} with tolfenamic acid in goats (Sidhu *et al* 2010) [15].

These findings indicate that there was a significant decrease in the AUC when marbofloxacin was given along with the meloxicam. That is, higher the clearance, the lesser is the time spent by the drug in the systemic circulation and rapid decline in the plasma drug concentration. Since the clearance of marbofloxacin is significantly high and reduced elimination half life with meloxicam in the present study the value of AUC is significantly reduced. Similarly, Anjana *et al* (2017) [18] also reported that meloxicam was likely to reduce the AUC value of moxifloxacin in goats.

MRT of marbofloxacin when administered at 2 mg.kg^{-1} body weight was reported as 9.70 h in buffalo calves (Baroni *et al*

2010) [13], 5.33 h in calves (AliAbadi and Lees 2002) [16], 6.1 ± 0.8 h in calves (Ismail and El-Kattan 2007) [17], 5.44 ± 1.23 h in goats (Waxman *et al* 2001) [19] and 4.23 h in goats (Sidhu *et al* 2010) [15].

In the present study, MRT was found to be 4.64 ± 0.2 h when marbofloxacin was given along with meloxicam. Similar findings were reported earlier i.e 11.66 h with ketoprofen in buffalo calves (Baroni *et al* 2010) [13], 13.68 h with flunixin meglumine in buffalo calves (Baroni *et al* 2011) [14] and 4.495 h with tolfenamic acid in goats (Sidhu *et al* 2010) [15].

The present findings are however significantly reduced as compared to the MRT findings of Baroni *et al* (2010) [13] in marbofloxacin group. Since the elimination half life, clearance, area under curve of the present study are significantly deviated from the referred values as discussed earlier, so it's likely that meloxicam affects the MRT value of marbofloxacin when administered concomitantly. It could possibly be because meloxicam may affect the entero-hepatic recirculation of the marbofloxacin thereby significantly altering the MRT values.

Pharmacokinetic surrogates or Predictors of efficacy of marbofloxacin when co-administered with meloxicam.

In the present study the AUC_{0-12} value was 5.47 µg.h.ml^{-1}, C_{max} value was 1.19 µg.ml^{-1}. The C_{max}/MIC and AUC/MIC of the present study is represented in Table 3.

Table 3: The values of surrogates C_{max}/MIC and AUC/MIC of marbofloxacin with meloxicam against respective MIC of certain bacterial species

Bacteria	MIC^	C_{max} (µg.ml^{-1})	AUC_{0-12} (µg.h.ml^{-1})	C_{max}/MIC (Ratio)	AUC/MIC (h)
*K pneumonia**	0.032	1.19	5.47	37.18	170.93
*M haemolytica***	0.04	1.19	5.47	29.75	136.75
*Salmonella spp****	0.073	1.19	5.47	16.30	74.93
*P multocida***	0.56	1.19	5.47	2.13	9.76

^Source of MIC values: * - ATCC 43816 (Kesteman *et al* 2009) [20]; ** - Bovine isolates (AliAbadi and Lees 2002) [61]; *** - Bovine isolates (Meunier *et al* 2004) [21].

Table 4: The values of surrogates C_{max}/MIC and AUC/MIC of marbofloxacin with meloxicam against respective MIC of certain bacterial species compared with the findings of Baroni *et al* 2010 for marbofloxacin alone in buffalo calves.

Bacteria	C_{max}/MIC (Ratio)	AUC/MIC (h)	C_{max}/MIC	AUC/MIC (h)
K pneumonia	37.18	170.93	40.91	389
M haemolytica	29.75	136.75	32.73	311
Salmonella spp	16.30	74.93	17.93	170
P multocida	2.13	9.76	0.56	22

The surrogate's values in the Table-4 against MIC of the respective bacterial species showed some significant changes from the values when compared with the findings of Baroni *et al* (2010) in Table 13. C_{max}/MIC values for the given bacteria remained greater than 10 (Drusano *et al* 1993; Preston *et al* 1998) [22, 23] and AUC_{0-12} /MIC was more than 125 (Forrest *et al* 1993) [24] except for *Pasteurella multocida*. but AUC_{0-12} /MIC values reduced by more than half as compared to the findings of Baroni *et al* (2010) [13] indicating that the meloxicam decreases the bactericidal potential of marbofloxacin.

By these findings, the study concludes that the dose of marbofloxacin (8 mg.kg^{-1}) administered i.m, along with meloxicam (0.5 mg.kg^{-1}) in buffalo calves was found effective against the bacterial pathogens with MIC value of 0.073 µg.ml^{-1}. Hence the present study suggests that meloxicam affects the pharmacokinetic parameters of marbofloxacin when administered intramuscularly in buffalo calves.

Ultimately, it is the integrity of the host immune response and the physiology of the animal which determine the efficacy and effectiveness of the targeted pharmacokinetic-pharmacodynamic relationship.

Conclusions

Findings of the study may prove beneficial in recommendation of dosage regimen for the judicious, efficacious and safe use of marbofloxacin along with meloxicam. Studies on the influence of the NSAIDs on the disposition of marbofloxacin may help in understanding in making recommendation for altered dosage interval in buffalo calves. Meloxicam is likely to alter the pharmacokinetic parameters of marbofloxacin in buffalo calves remarkably. Marbofloxacin (8 mg.kg^{-1}) administered i.m, in combination with meloxicam (0.5 mg.kg^{-1}) in buffalo calves was effective against the bacterial pathogens with MIC values of 0.073 µg.ml^{-1}.

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References

1. Spreng M, Deleforge J, Thomas V, Boisrame B, Drugeon H. Antibacterial activity of marbofloxacin. A new fluoroquinolone for veterinary use against canine and feline isolates. Journal of Veterinary Pharmacology and Therapeutics. 1995;18(4):284-89.
2. Brown SA. Fluoroquinolones in animal health. Journal of Veterinary Pharmacology and Therapeutics. 1996;19(1):1-14.
3. Elzoghby R, Aboubakr M. Pharmacokinetics, urinary excretion and milk penetration of marbofloxacin in lactating buffaloes. Journal of American Science. 2015;11(4):23-28.
4. Dalhoff A. *In vitro* activities of quinolones. Expert Opinion on Investigational Drugs. 1999;8(2):123-37.
5. Smith GW, Davis JL, Tell LA, Webb AI, Riviere JE. Extralabel use of nonsteroidal anti-inflammatory drugs in cattle. Journal of the American Veterinary Medical Association. 2008;232(5):697-01.

6. Ogino K, Hatanaka K, Kawamura M, Katori M, Harada Y. Evaluation of pharmacological profile of meloxicam as an anti-inflammatory agent with particular reference to its relative selectivity for cyclooxygenase-2 over cyclooxygenase-1. Pharmacology. 1997;55(1):44-53.
7. Coetzee JF, Mosher RA, Griffith GR, Gehring R, Anderson DE, KuKanich B *et al*. Pharmacokinetics and tissue disposition of meloxicam in beef calves after repeated oral administration. Journal of Veterinary Pharmacology and Therapeutics. 2015;38(6):556-62.
8. Sidhu PK, Landoni MF, Aliabadi FS, Lees P. Pharmacokinetic and pharmacodynamic modelling of marbofloxacin administered alone and in combination with tolfenamic acid in goats. The Veterinary Journal. 2010;184(2):219-29.
9. Dumka VK, Srivastava AK. Disposition kinetics, urinary excretion and dosage regimen of levofloxacin formulation following single intravenous administration in crossbred calves. Veterinary Research Communications. 2007;31(7):873-79.
10. Ahmed FA, Mohan P, Barua CC, Dutta DJ. Effect of intramuscular diclofenac sodium on pharmacokinetics of intravenous enrofloxacin in calves. Indian Journal of Pharmacology 2005;37(3):189.
11. Rahal A, Kumar A, Ahmad AH, Malik JK. Pharmacokinetics of diclofenac and its interaction with enrofloxacin in sheep. Research in Veterinary Science. 2008;84(3):452-56.
12. Derendorf H, Meibohm B. Modeling of pharmacokinetic/pharmacodynamic (PK/PD) relationships: concepts and perspectives. Pharmaceutical Research. 1999;16(2):176-85.
13. Baroni EE, Rodríguez C, San Andrés MD, Moroni C, Rubio S, De Lucas JJ *et al*. Influence of ketoprofen on the pharmacokinetics of marbofloxacin in buffalo calves (Preliminary study). Revista Veterinaria. 2010;21(1):314-16
14. Baroni EE, Rubio S, Rodríguez C, De Lucas JJ, Fernández H, Andrés MS. Pharmacokinetic interactions of marbofloxacin with anti-inflammatory drugs in buffalo calves. Veterinary Record. 2011;169(7):182.
15. Sidhu PK, Landoni MF, Aliabadi FS, Lees P. Pharmacokinetic and pharmacodynamic modelling of marbofloxacin administered alone and in combination with tolfenamic acid in goats. The Veterinary Journal. 2010;184(2):219-29.
16. AliAbadi FS, Lees P. Pharmacokinetics and pharmacokinetic/ pharmacodynamic integration of marbofloxacin in calf serum, exudate and transudate. Journal of Veterinary Pharmacology and Therapeutics. 2002;25(3):161-74.
17. Ismail M, El-Kattan YA. Comparative pharmacokinetics of marbofloxacin in healthy and *Mannheimia haemolytica* infected calves. Research in Veterinary Science. 2007;82:398-04.
18. Anjana K, Mody SK, Nirala RK, Kumari A. Effect of meloxicam on pharmacokinetics of long acting moxifloxacin in Goats. International Journal of Current Microbiology and Applied Sciences. 2017;6(3):1104-08.
19. Waxman S, Rodríguez C, González F, De Vicente ML, San Andrés MI, San Andrés MD. Pharmacokinetic behavior of marbofloxacin after intravenous and intramuscular administrations in adult goats. Journal of Veterinary Pharmacology and Therapeutics. 2001;24:375-78.
20. Kesteman AS, Ferran AA, Perrin-Guyomard A, Laurentie M, Sanders P, Toutain PL *et al*. Influence of inoculum size and marbofloxacin plasma exposure on the amplification of resistant subpopulations of Klebsiella pneumoniae in a rat lung infection model. Antimicrobial Agents and Chemotherapy 2009;53(11):4740-48.
21. Meunier DD, Acar JF, Martel JL, Kroemer S, Valle M. Seven years survey of susceptibility to marbofloxacin of bovine pathogenic strains from eight European countries. International Journal of Antimicrobial Agents. 2004;24(3):268-78.
22. Drusano GL, Johnson DE, Rosen M, Standiford HC. Pharmacodynamics of a fluoroquinolone antimicrobial agent in a neutropenic rat model of Pseudomonas sepsis. Antimicrobial Agents and Chemotherapy. 1993;37(3):483-90.
23. Preston SL, Drusano GL, Berman AL, Fowler CL, Chow AT, Dornseif B, *et al*. Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. Journal of the American Medical Association. 1998;279:125-29.
24. Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrobial Agents and Chemotherapy. 1993;37:1073-81.
25. Baroni EE, Rodríguez C, San Andrés MD, Moroni C, Rubio S, De Lucas JJ *et al*. Influence of ketoprofen on the pharmacokinetics of marbofloxacin in buffalo calves (Preliminary study). Revista Veterinaria. 2010;21(1):314-16.