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ORIGINAL ARTICLE

Influences of tolfenamic acid and flunixin meglumine on the disposition kinetics of levofloxacin in sheep

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ABSTRACT

The pharmacokinetics of levofloxacin (4 mg/kg), administered both alone and in combination with tolfenamic acid (2 mg/kg) and flunixin meglumine (2.2 mg/kg), was established after intravenous administration in sheep. Plasma levofloxacin concentrations were assayed by high-performance liquid chromatography and analysed according to the two-compartment open model. Following the administration of levofloxacin alone, the mean distribution half-life, elimination half-life, total clearance, volume of distribution at steady state and area under the plasma concentration–time curve were 0.20 h, 1.82 h, 0.39 L/h/kg, 0.96 L/kg and 10.40 h × μg/mL, respectively. Tolfenamic acid and flunixin meglumine caused a slow elimination and increased plasma concentrations of levofloxacin in combination administration. Levofloxacin, with an alteration in the dosage regimen, can be used effectively with tolfenamic acid and flunixin meglumine for the therapy of infections and inflammatory conditions in sheep.

KEYWORDS

levofloxacin, tolfenamic acid, flunixin meglumine, pharmacokinetics, sheep

INTRODUCTION

The development of resistance to fluoroquinolones in human and animal pathogens has raised suspicion regarding the rational use of antibiotics in food animals (Pallo-Zimmerman et al., 2010). The resistance resulting from the incorrect and inappropriate use of antibiotics in animals leads to treatment failure and significant unfavourable outcomes in animal health and welfare (CVMP, 2007). The transfer of resistant zoonotic bacteria from animals to humans through the food chain may cause gastrointestinal tract infections in humans (WHO, 1998). The isolation of fluoroquinolone-resistant strains of *Campylobacter, Salmonella* and *Escherichia coli* has been reported in humans (Pallo-Zimmerman et al., 2010). Fluoroquinolones must be used at an appropriate dosage regimen in target species to prevent the development of resistance to fluoroquinolone antibiotics and ensure their safe use in both humans and animals (WHO, 1998; CVMP, 2007).

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Levofloxacin, a levo isomer of ofloxacin, is a second-generation fluoroquinolone antibiotic. It exerts bactericidal effects by inhibiting DNA gyrase and topoisomerase IV. Levofloxacin has a broad spectrum of activity against Gram-positive, Gram-negative and atypical bacteria (Norrby, 1999; Zhanel and Noreddin, 2001). The antimicrobial activity of levofloxacin against *Streptococcus pneumoniae, Chlamydia pneumoniae* and *Mycoplasma pneumoniae* is higher than that of other fluoroquinolone antibiotics (Zhanel and Noreddin, 2001; Bakken, 2004). Levofloxacin also exerts post-antibiotic effects against *Staphylococcus aureus*, *E. coli* and *Pseudomonas aeruginosa* (Norrby, 1999). It is used in the treatment of pneumonia, acute bacterial exacerbations of chronic bronchitis, acute sinusitis, urinary tract infections, pyelonephritis and skin infections in humans (North et al., 1998). The use of fluoroquinolones in animals is recommended for the treatment of mastitis, metritis and respiratory and gastrointestinal tract infections (WHO, 1998).

Pharmacodynamic and pharmacokinetic data are used to determine the appropriate dosage regimens of antibiotics. Levofloxacin is a concentration-dependent antimicrobial agent, and the area under the plasma concentration–time curve (AUC)/minimum inhibitory concentration (MIC) ratio is used to evaluate its antimicrobial activity. Therefore, changes in the pharmacokinetics of levofloxacin may change its therapeutic efficacy (Odenholt and Cars, 2006). The concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics is recommended for the treatment of inflammatory conditions in animals (Neuman, 1987; Deleforge et al., 1994). However, in concomitant use, pharmacokinetic and drug–drug interactions may arise that usually vary across animal species, and therefore these should be studied in the target animals (Ogino et al., 2005; Ogino and Arai, 2007; Abo El-Sooud and Al-Anati, 2011). Flunixin meglumine and tolfenamic acid can be concurrently administered with levofloxacin to treat inflammatory conditions caused by bacterial infections in sheep. However, our literature review revealed no study on the effects of flunixin meglumine and tolfenamic acid on the pharmacokinetics of levofloxacin. Therefore, the present study aimed to determine the influences of flunixin meglumine and tolfenamic acid on the pharmacokinetics of levofloxacin in sheep.

MATERIALS AND METHODS

Drugs and chemicals

Levofloxacin analytic standards (≥ 98%) were obtained from Sigma Aldrich (St. Louis, MO, USA). The solvents (Merck Limited, Darmstadt, Germany) used during the chromatographic analysis of the drug were of high-performance liquid chromatography (HPLC) grade. Levofloxacin (Tavanic, 500 mg/100 mL, Sanofi Aventis, Istanbul, Turkey), tolfenamic acid (Tolfine, 40 mg/mL, Novakim, Kocaeli, Turkey) and flunixin meglumine (Finadyne, 50 mg/mL, MSD Animal Health) were purchased from the manufacturer.

Animals

Six clinically healthy Akkaraman sheep, weighing 48 ± 6 kg and aged 1.5–2.4 years, were used in this study. Sheep that had no disease history and were determined to be healthy based on physical examination, complete blood count and serum biochemistry panel were included in the study. The animals were housed in individual pens separated by wire mesh barriers. All sheep were provided a standard ration, and free access to hay and water. The study was conducted following a one-week acclimatization period. The study protocol (2017/130) was approved by the Ethical Committee of the Faculty of Veterinary Medicine of Selcuk University, Turkey.

Experimental design

The study was carried out according to a 3-period, 3-treatment longitudinal design with a washout period of 15 days. At the beginning of the study, a catheter was placed into the right and left jugular veins of sheep for drug administration and blood collection, respectively. Levofloxacin (4 mg/kg, Goudah and Hasabelnaby, 2010), tolfenamic acid (2 mg/kg, Corum et al., 2018; Yildiz et al., 2019), and flunixin meglumine (2.2 mg/kg, Welsh et al., 1993) were administered to the sheep as a single IV bolus through the venous line placed in the right jugular vein. In the first period, only levofloxacin was administered to the sheep. Then, levofloxacin + tolfenamic acid was administered in the second period, and levofloxacin + flunixin meglumine in the third period. In the combination groups, levofloxacin was administered within approximately 1 min following tolfenamic acid or flunixin meglumine administration. Following levofloxacin administration in each period, blood samples (approximately 2 mL) from the left jugular vein of each sheep were collected into heparinised tubes before drug administration (0 h) and at 0.08, 0.17, 0.25, 0.33, 0.42, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18 and 24 h after drug administration. Blood samples were centrifuged at 4,000 g for 10 min, and plasma samples were stored at −80 °C until analysis.

Analysis of levofloxacin

The plasma concentration of levofloxacin was measured using a HPLC-UV method reported previously (Czyrski and Szałek, 2016). Four hundred μL of methanol containing 0.1% TFA was added to 200 μL of plasma and the solution was vortexed for 30 s. After centrifugation at 10,000 g for 10 min, 200 μl of the clear supernatant was decanted to autosampler vials, and 10 μl supernatant was injected into the HPLC system. The HPLC system (Shimadzu, Tokyo, Japan) comprised a pump (LC-20AT) controlled by the CBM-20A system (LC-20AT), an autosampler (SIL-20A), a degasser (DGU-20A), a column oven (CTO-10A), and an SPD-20A UV-VIS detector with the LC Solution software program (Shimadzu, Japan). Chromatographic separations were performed using a reverse phase Gemini™ C18 column (250 × 4.6 mm; internal diameter, 5 μm; Phenomenex, Torrance,

CA) at 30 °C temperature. The UV light detector was set at 290 nm. The mobile phase consisted of acetonitrile, and 1% triethylamine adjusted to pH 2.5 using orthophosphoric acid (15:85, v/v), and the flow rate was 1.0 mL/min.

A stock solution of levofloxacin at 1 mg/mL concentration was prepared in pure water and stored at –70 °C. Standard working solutions of levofloxacin prepared daily were used to spike blank plasma samples of sheep. Levofloxacin quantitation was linear (>0.9996) within the range of 0.02–10 μg/mL. The quality control samples of levofloxacin prepared at 0.1 μg/mL (low), 1 μg/mL (medium) and 10 μg/mL (high) concentrations were used to determine the recovery, precision and accuracy of the HPLC method. The recovery of levofloxacin in sheep plasma was in the range of 95–104%. The limit of detection and the limit of quantification in plasma for levofloxacin were 0.01 and 0.02 μg/mL, respectively. The intra- and inter-day assay coefficients of variation were <8%. The intra- and inter-day assay biases were ±6%.

Pharmacokinetic analysis

Pharmacokinetic parameters were calculated based on levofloxacin concentrations by the use of compartmental methods with a WinNonlin 6.3 software (Pharsight, Certara, St. Louis, MO, USA). The appropriate pharmacokinetic model was evaluated by visual examination of individual concentration–time curves and based on Akaike's information criteria (Yamaoka et al., 1978). The pharmacokinetic variables of levofloxacin in each sheep were analysed according to the two-compartment open model. Pharmacokinetic parameters, that is area under the plasma concentration–time curve (AUC), distribution half-life ($t_{1/2\alpha}$), elimination half-life ($t_{1/2\beta}$), mean residence time (MRT), total clearance (Cl_T), volume of distribution at steady state (V_{dss}), rate of transfer from central to peripheral compartment (k_{12}), rate of transfer from peripheral to central compartment (k_{21}), elimination rate constant (β) and distribution rate constant (α), were calculated by the software program.

Statistical analysis

Statistical analyses were carried out using SPSS 22.0 statistical program (IBM Corp., Armonk, NY). All data were presented as mean ± SD. $t_{1/2\alpha}$, $t_{1/2\beta}$ and MRT were shown as harmonic mean ± SD. For $t_{1/2\alpha}$, $t_{1/2\beta}$ and MRT, the differences between treatment groups were determined by using the Wilcoxon's Rank Sum test. Statistical differences between groups in other pharmacokinetic parameters were analysed by one-way analysis of variance and the *post hoc* Tukey test. Statistical significance was accepted at $P < 0.05$.

RESULTS

The semi-logarithmic plasma concentration–time curves and pharmacokinetic parameters obtained after intravenous administration of levofloxacin alone and co-administered with tolfenamic acid or flunixin meglumine in sheep are presented in Fig. 1 and Table 1, respectively. The plasma concentration of levofloxacin, when administered alone and in combination with tolfenamic acid and flunixin meglumine, was 5.47 μg/mL, 6.68 μg/mL and 7.11 μg/mL, respectively, at the time of the first sampling (0.08 h). Levofloxacin was detectable until 12 h following a single-dose administration and detectable until 18 h and 24 h following co-administration with tolfenamic acid or flunixin meglumine, respectively. Tolfenamic acid administration changed the $t_{1/2\beta}$, $t_{1/2\alpha}$, MRT, Cl_T, V_{dss} and AUC of levofloxacin by 23%, –30%, 23%, –31%, –14% and 41%, respectively ($P < 0.05$). Flunixin meglumine administration changed the $t_{1/2\beta}$, $t_{1/2\alpha}$, MRT, Cl_T, V_{dss} and AUC of levofloxacin by 78%, –10%, 80%, –51%, –11% and 103%, respectively ($P < 0.05$). After combined administration with tolfenamic acid or flunixin meglumine, the k_{21}/k_{12} and k_{12}/k_{21} ratios of levofloxacin increased and decreased, respectively ($P < 0.05$).

DISCUSSION

The plasma concentration–time curves of levofloxacin after its IV injection were best fitted to a two-compartmental open model in all the animals. Although the plasma concentration–time curves of levofloxacin in sheep (Goudah and Hasabelnaby, 2010) and camels (Goudah, 2009) best fit to the two-compartment open model, some studies in sheep (Patel et al., 2012) and rabbits (Czyrski et al., 2015) have been performed with noncompartmental analysis.

The co-administration of tolfenamic acid or flunixin meglumine with levofloxacin significantly decreased the Cl_T of levofloxacin by 30% and 51%, respectively. Levofloxacin undergoes minimal metabolism and 57–86% is excreted through glomerular filtration and tubular secretion in the kidneys (Hurst et al., 2002; Hemeryck et al., 2006). Tolfenamic acid and flunixin meglumine are converted to conjugated metabolites in the liver and excreted in the urine and faeces (CVMP, 1997; CVMP, 1999). The decrease caused in the Cl_T of levofloxacin by tolfenamic acid or flunixin meglumine, observed in the present study, may occur for two reasons. Firstly, tolfenamic acid or flunixin meglumine might inhibit prostaglandin synthesis in the kidneys (Hörl, 2010) and, thereby, reduce the blood flow to the kidneys as well as the glomerular filtration rate. Secondly, the renal clearance rate of levofloxacin is 60% higher than that of creatinine and, therefore, levofloxacin is excreted via glomerular filtration and tubular secretion (Martinez et al., 2006). Certain organic cation (OCT) and organic anion transport (OAT) systems play a role in the tubular secretion of levofloxacin (Yano et al., 1997). Although tolfenamic acid and flunixin meglumine are not known to have an effect on the OCT and OAT systems, some NSAIDs have reportedly demonstrated an inhibitory effect (Khamdang et al., 2002). The decrease in the Cl_T of levofloxacin may be caused by the above-mentioned factors. Cimetidine and probenecid have also been reported to decrease the Cl_T of levofloxacin by 24–

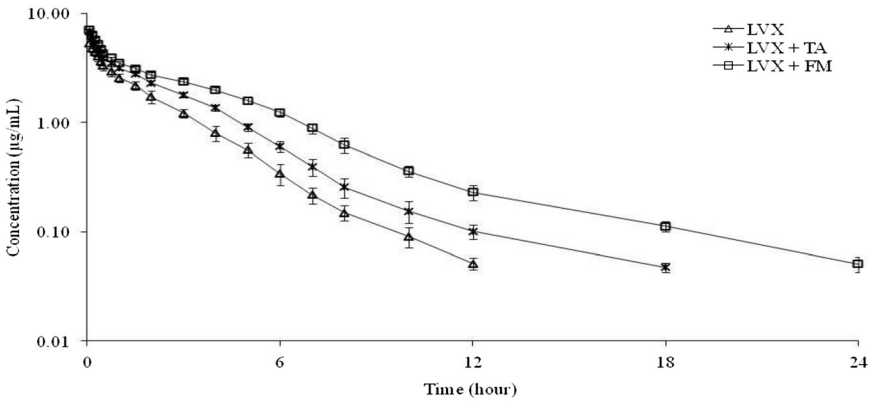

Figure 1. Semi-logarithmic plasma concentration–time curves of levofloxacin (LVX) after intravenous bolus injection (4 mg/kg) alone and co-administered with tolfenamic acid (TA, 2 mg/kg) or flunixin meglumine (FM, 2.2 mg/kg) in sheep (mean ± SD, $n = 6$)

35% through the inhibition of tubular secretion (Aminimanizani et al., 2001). Tolfenamic acid and flunixin meglumine substantially decreased the V_{dss} of levofloxacin. Moreover, the binding capacity of levofloxacin to plasma proteins is low (20–40%, Aminimanizani et al., 2001), and it varies depending on the plasma drug concentration (Sheikh et al., 2001). In the present study, tolfenamic acid or flunixin meglumine administration increased the plasma concentration of levofloxacin at the first sampling time point (0.08 h) from 5.26 µg/mL to 6.76–7.03 µg/mL. The decreased V_{dss} of levofloxacin could be caused by the increased binding of levofloxacin to plasma proteins as a result of its increasing concentration. Tolfenamic acid and flunixin meglumine prolonged the $t_{1/2\beta}$ of levofloxacin by 23% and 78%, and this prolonged $t_{1/2\beta}$, despite a decrease in the V_{dss} of levofloxacin, may be caused by decreased Cl_T. However, tolfenamic acid does not affect the apparent volume of distribution and the elimination of cefquinome in sheep (Rana et al., 2015).

The co-administration of tolfenamic acid or flunixin meglumine with levofloxacin increased the k_{12}/k_{21} ratio and decreased the k_{21}/k_{12} ratio of levofloxacin ($P < 0.05$). An increased k_{12}/k_{21} ratio suggests accelerated transport of levofloxacin from the central compartment to the peripheral compartment, possibly because of the decreased elimination or increased plasma concentration of levofloxacin. A change in the plasma concentration–time profile of levofloxacin following co-administration may have changed the AUC. Tolfenamic acid or flunixin meglumine administration increased the AUC of levofloxacin by 41% and 103%, respectively. Similar results have been reported with the co-administration of diclofenac and naproxen with tetracycline in rats (Oh and Han, 2006). The decrease in the k_{21}/k_{12} ratio following co-administration may be caused by a balance between plasma and tissue drug concentrations.

The antibacterial effect of levofloxacin is concentration dependent, and its bactericidal activity increases with increasing doses. The AUC/MIC ratio is considered while evaluating the antibacterial effect of levofloxacin. For the effective eradication of bacteria and good clinical outcomes,

Table 1. Pharmacokinetic parameters (mean ± SD) obtained after intravenous administration of levofloxacin (4 mg/kg) alone and co-administered with tolfenamic acid (2 mg/kg) or flunixin meglumine (2.2 mg/kg) in sheep ($n = 6$)

Parameter	Levofloxacin	Levofloxacin + Tolfenamic Acid	Levofloxacin + Flunixin Meglumine
k_{12} (1/h)	0.98 ± 0.05[b]	1.94 ± 0.40[a]	1.55 ± 00.19[a]
k_{21} (1/h)	2.25 ± 0.15[b]	2.72 ± 0.28[a]	2.09 ± 0.16[b]
k_{12}/k_{21}	0.43 ± 0.02[b]	0.71 ± 0.11[a]	0.75 ± 0.11[a]
k_{21}/k_{12}	2.31 ± 0.13[a]	1.44 ± 0.25[b]	1.36 ± 0.20[b]
α (1/h)	3.42 ± 0.18[b]	4.91 ± 0.66[a]	3.82 ± 0.24[b]
β (1/h)	0.38 ± 0.01[a]	0.31 ± 0.02[b]	0.21 ± 0.01[c]
$t_{1/2\alpha}$ (h) (HM)	0.20 ± 0.01[a]	0.14 ± 0.02[c]	0.18 ± 0.01[b]
$t_{1/2\beta}$ (h) (HM)	1.82 ± 0.05[c]	2.23 ± 0.12[b]	3.24 ± 0.13[a]
MRT (h) (HM)	2.48 ± 0.07[c]	3.05 ± 0.16[b]	4.46 ± 0.17[a]
AUC (h × µg/mL)	10.40 ± 1.17[c]	14.71 ± 0.59[b]	21.11 ± 1.35[a]
Cl_T (L/h/kg)	0.39 ± 0.04[a]	0.27 ± 0.01[b]	0.19 ± 0.01[c]
V_{dss} (L/kg)	0.96 ± 0.08[a]	0.83 ± 0.04[b]	0.85 ± 0.04[b]

[a,b,c]Varied characters in the same row are statistically different ($P < 0.05$).

k_{12}, rate of transfer from central to peripheral compartment; k_{21}, rate of transfer from peripheral to central compartment; α, distribution rate constant; β, elimination rate constant; $t_{1/2\alpha}$, distribution half-life; $t_{1/2\beta}$, elimination half-life; MRT, mean residence time; AUC, area under the plasma concentration–time curve; Cl_T, total clearance; V_{dss}, volume of distribution at steady state; HM, harmonic mean.

the AUC/MIC ratio of levofloxacin for Gram-positive and Gram-negative bacteria must be ≥30 and ≥100, respectively. The demonstration of these ratios during the treatment suggests >80% clinical efficacy of the treatment (Nightingale et al., 2000). Gram-negative (such as *Pasteurella multocida, E. coli* and *Salmonella* spp.) and Gram-positive (such as *S. pneumoniae*) bacteria cause pneumonia, diarrhoea, abortion and abscesses in sheep (Myers et al., 1984; Bell, 2008). To the best of our knowledge, the MIC value of levofloxacin for these bacterial strains isolated from sheep has not yet been determined. However, the reported MIC value of levofloxacin for Gram-negative and Gram-positive bacteria isolated from humans is ≤0.12 and ≤2 μg/mL, respectively (Marshall and Jones, 1993; Davis and Bryson, 1994). The administration of levofloxacin (4 mg/kg) alone did not achieve an AUC/MIC ratio of ≥100 for the above-mentioned Gram-negative bacteria, whereas co-administration with tolfenamic acid or flunixin meglumine achieved the desired level, as demonstrated in this study. Levofloxacin alone and in co-administration did not achieve an AUC/MIC ratio of ≥30 that is recommended for *S. pneumoniae*; however, an AUC/MIC ratio of ≥30 can be achieved for Gram-positive bacteria with a MIC value of ≤0.35 μg/mL for levofloxacin, ≤ 0.49 μg/mL for levofloxacin + tolfenamic acid, and ≤0.70 μg/mL for levofloxacin + flunixin meglumine.

In conclusion, tolfenamic acid and flunixin meglumine caused slow elimination and increased plasma concentrations of levofloxacin in sheep. Levofloxacin, with an alteration in its dosage regimen, can be used effectively with tolfenamic acid and flunixin meglumine for the therapy of infections and inflammatory conditions in sheep. However, the *in vitro* and *in vivo* antibacterial efficacy of levofloxacin against pathogens isolated from sheep needs to be determined. In addition, levofloxacin should be administered in accordance with prudent use guidelines in order to sustain its high therapeutic value.

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