VETERINARSKI ARHIV 85 (3), 283-292, 2015

Effect of tolfenamic acid co-administration on pharmacokinetics of cefquinome following intramuscular administration in sheep

Mayankkumar P. Rana, Kamlesh A. Sadariya*, and Aswin M. Thaker

Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Anand Agricultural University, Anand, Gujarat, India

RANA, M. P., K. A. SADARIYA, A. M. THAKER: Effect of tolfenamic acid co-administration on pharmacokinetics of cefquinome following intramuscular administration in sheep. Vet. arhiv 85, 283-292, 2015.

ABSTRACT

The pharmacokinetics of cefquinome (2 mg/kg) were studied following intramuscular administration of cefquinome alone, and co-administered with tolfenamic acid (2 mg/kg) in sheep. The plasma concentration of cefquinome was detected by High Performance Liquid Chromatography. Following a single dose intramuscular administration of cefquinome alone, the peak plasma concentration (C_{max}) was 4.36 ± 0.10 µg/mL obtained at 0.75 h. The absorption half-life ($t_{1/2K\alpha}$), volume of distribution (Vd_{area}), total body clearance (Cl_B) and elimination half-life ($t_{1/2\beta}$) of cefquinome were 0.61 ± 0.10 h,2.07 ± 0.36 L/kg, 0.12 ± 0.01 L/h/kg and 12.29 ± 2.62 h, respectively. Following intramuscular co-administration of tolfenamic acid, no significant changes were observed in most of the pharmacokinetic parameters of cefquinome, except C_{max} and the absorption rate constant (K_a) were significantly increased, while $t_{1/2\ K\alpha}$ was significantly reduced compared to cefquinome alone treatment of sheep. Cefquinome pharmacokinetic data (2 mg/kg) generated from the present study suggest that cefquinome may be administered with tolfenamic acid to treat bacterial infection with inflammatory conditions in sheep.

Key words: pharmacokinetics, cefquinome, tolfenamic acid, sheep

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed with antibacterial agents in multiple drug prescriptions. Cefquinome is the first animal dedicated, fourth generation cephalosporin antibiotic having a broad spectrum of activity. The zwitterionic property of cefquinome facilitates rapid penetration across the biological membranes, including the porins of the bacterial cell wall, enhancing bioavailability and improving the spectrum of antimicrobial activity, compared with second and third

*Corresponding author:

Dr. K. A. Sadariya, M.V.Sc., Ph.D., Assistant Professor, Department of Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Anand Agricultural University, Anand-388001, Gujarat, India, Phone: +91 9427 180817; Phone & Fax: +91 2692 261486; E-mail: dr_kasadariya@yahoo.co.in

ISSN 0372-5480
Printed in Croatia

generations cephalosporins (SADER and JONES, 1993; SHPIGEL and SCHMID, 1997; GUERIN-FAUBLEE et al., 2003; THOMAS et al., 2002). Tolfenamic acid (TA) is an NSAID of the fenamate group with excellent anti-inflammatory, analgesic, anti-pyretic activities, and anti-endotoxaemic properties (REJHOLEC et al., 1979). It inhibits the biosynthesis of prostaglandins and also has an inhibitory action on prostaglandin receptors. Moreover, it also produces inhibition of cyclooxygenase and lipoxygenase (LINDEN et al., 1976; PROUDMAN and McMILLAN, 1991; KANKAANRANTA et al., 1991). NSAIDs are frequently recommended as an adjunct therapy with antibacterial, to treat various bacterial infections accompanied by many inflammatory conditions in animals. A higher volume of distribution of tolfenamic acid was found in the marbofloxacin-treated calves (SIDHU et al., 2005). Co-administration of several drugs often results in unpredictable therapeutic outcome. Hence, this study was conducted to recommend the clinical use of cefquinome in combination with tolfenamic acid in the treatment of susceptible bacterial diseases affecting sheep. Cefquinome is stable against chromosomally and plasmid-encoded lactamases produced by the majority of clinically important bacteria (LIMBERT et al., 1991). Pharmacokinetic studies of cefquinome have been conducted in buffalo calves (DINAKARAN et al., 2013), goats (DUMKA et al., 2013), chickens (XIE et al., 2013), piglets (SONG et al., 2013), sheep (UNEY et al., 2011; TOHAMY et al., 2011), ducks (YUAN et al., 2011), rabbit (HWANG et al., 2011), horses (WINTHER et al., 2011), camels (AL-TAHER, 2010) and pigs (YANG et al., 2009).

However, there is no information available on the influence of the co-administration of tolfenamic acid on the pharmacokinetics of cefquinome in animals. So, the present study was conducted to investigate the influence of tolfenamic acid on the pharmacokinetics of cefquinome in sheep.

Materials and methods

Drug and chemicals. Cefquinome technical grade pure powder was procured from Sigma-Aldrich, India; Cefquinome suspension (25 mg/50 mL; Cobactan® 2.5 %, Intervet India Pvt. Ltd., Pune, India) and tolfenamic acid injections (40 mg/mL; Maxxtol®, Intas Pharmaceutical Ltd. Ahmedabad, India) were purchased on the market. Acetonitrile, methanol, trifluroacetic acid and perchloric acid (about 70 %) (Analytical grade) and water of HPLC grade were purchased from Merck Limited, Mumbai, India.

Experimental animals. The experiment was conducted on six healthy adult (2-3 years of age) Patanwadi sheep, weighing 28-32 kg. Each sheep was housed in a separate pen and provided *ad libitum* water and standard ration. The sheep were kept under constant observation for two weeks before the commencement of the experiment and all necessary managerial procedures were adopted to keep the animals free from stress.

The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC No. 2012/VPT/135).

Experimental design. The study was carried out in cross-over design, with a minimum of 15 days of washout period. All six animals were randomly allocated to receive a single intramuscular injection of cefquinome (2 mg/kg, body mass) alone, or co-administered with intramuscular administration of tolfenamic acid (2 mg/kg, body mass). Both the drugs were administered one by one in the co-administered group within a few seconds. A washout period of 2 weeks was observed between treatments. Intramuscular injection was given into the deep gluteal muscles, using a 20 G ×25 mm needle. Blood samples (2 mL) were collected in sterile heparinized vials at 0 minute (before drug administration) 5, 10, 15, 30 and 45 minutes and at 1, 2, 4, 8, 12, 18, 24 and 36 hours after intramuscular administration. The sheep were monitored for any adverse reactions throughout the entire study period. Plasma was separated soon after collection by centrifugation at 3000 rpm for 10 minutes at 10 °C (Eppendorf 5804 R, Germany). Separated plasma samples were transferred to labeled cryovials and stored at -35 °C until assayed for cefquinome concentration, using the High Performance Liquid Chromatography (HPLC) procedure within 24 to 36 h.

Cefquinome assay

Instrumentation. Plasma cefquinome concentrations were quantified using reverse-phase High Performance Liquid Chromatography (HPLC), according to the method described by UNEY et al. (2011) with minor modifications. The HPLC system of Lab alliance (Scientific Systems, Inc., Lab Alliance, Pennsylvania, USA), comprising a quaternary gradient delivery pump (model AIS 2000) connected to an Autosampler (model Sykam S 5200, Sykam GmbH, Gewerbering, Eresing, Germany) and UV detector (model 500) was used for the assay.

Table 1. HPLC mobile-phase gradient conditions for analysis of cefquinome in sheep

Time (min)	Flow rate (mL/min)	% A (0.1 % Trifluoroacetic acid in water)	% B (Acetonitrile)
Initial	1.5	90	10
1	1.5	10	90
4	1.5	10	90
5	1.5	90	10

Chromatographic conditions. The mobile phase consisted of water containing 0.1 % trifluoroacetic acid as mobile phase A, and acetonitrile as mobile phase B in the gradient flow, as shown in Table 1. Chromatographic separation was performed using a reverse phase C18 column (PARTISIL 5 ODS-3 RAC-II; 4.6 ×100 mm ID, Whatman, Kent,

UK) at room temperature. HPLC data integration was performed using Clarity software (Version 2.4.0.190, Dataapex, Central Europe). The mobile phase was filtered through a 0.45 µm size filter (Ultipor N66 Nylone 6,6 membrane, PALL Pharmalab filtration Pvt., Ltd., Mumbai, India) and degassed by ultra-sonication. The mobile phase was pumped into the column at a flow rate of 1.5 mL/min at ambient temperature. The effluent was monitored at 270 nm wavelength.

Calibration curve. A calibration curve was prepared daily for drug concentrations ranging from 0.1 to 10 µg/mL, with mean correlation coefficient (r^2) >0.999. The limits of detection and limits of quantification were determined to be 0.05 and 0.1 µg/mL, respectively.

Sample extraction. Two hundred microliters (0.2 mL) of plasma were deproteinized by addition of methanol (400 µL) and vortexed for one minute. The mixture was vortexed for 1 minute and centrifuged at 10000 rpm for 5 minutes at 10 °C (Eppendorf 5804 R, Germany). The supernatant was decanted into a clean sterile micro centrifuge tube, and 20 µL supernatant was injected into the loop injector using the autosampler.

Validation of the assay method. The assay was sensitive and reproducible, and linearity was observed from 0.1 to 10 µg/mL ($r^2 = 0.999$). Plasma samples (n = 5) with the final concentrations of 0.25, 1, 2.5 and 5 µg/mL for cefquinome were extracted according to the procedure mentioned above. To fulfill the requirement of partial validation of the modified method, intra-day and inter-day precision and accuracy were evaluated. The intra-day assay precision and accuracy were estimated by analyzing six replicates at four different QC levels, i.e. 0.25, 1, 2.5 and 5 µg/mL. The assay values on both occasions (intra- and inter-day) were found to be within the accepted variable limits. Precision and accuracy of the assay, in conjunction with the linearity, indicates good accuracy of the assay with a coefficient of variance (C.V.) less than 9.13 %.

Pharmacokinetics analysis. The various pharmacokinetic parameters were calculated from plasma concentrations of cefquinome using software PK solution (version 2.0, summit research services, USA).

Statistical analysis. All the data are presented as mean ± S.E. Plasma concentrations and pharmacokinetic parameters were compared by the student's *t*-test, using SPSS software (version 12.0.1). Statistical significance was set at $P \leq 0.05$ and $P \leq 0.01$.

Results

No adverse effects or toxic manifestations were observed during the experimental period with regards to intramuscular administration of cefquinome (2 mg/kg) alone or co-administered with tolfenamic acid (2 mg/kg) in sheep. Plasma cefquinome concentrations at different time intervals following intramuscular injection alone and co-administered

intramuscularly with tolfenamic acid in sheep are presented as a semi logarithmic plot in Fig. 1. Non-compartmental pharmacokinetic analysis was performed using PK solution software, to calculate various pharmacokinetic parameters.

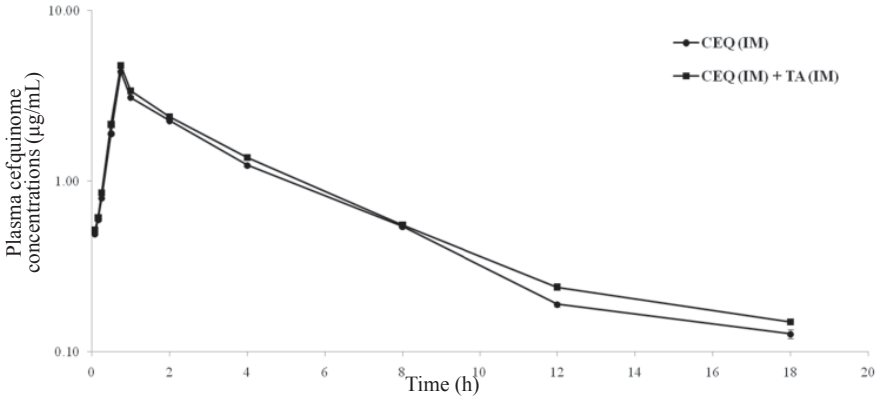

Fig. 1. Semi logarithmic plot of plasma cefquinome concentration versus time following intramuscular administration of cefquinome (2 mg/kg) alone and in tolfenamic acid treated (2 mg/kg) sheep. Each point represents mean ± SE of six animals.

Following intramuscular injection of cefquinome alone, the plasma concentration of cefquinome at 5 min was 0.49 ± 0.01 µg/mL, which gradually increased and reached the peak concentration (4.36 ± 0.10 µg/mL) at 45 min. On concurrent administration of tolfenamic acid and cefquinome, the initial plasma concentration of cefquinome at 5 min was 0.51 ± 0.01 µg/mL, which increased to attain the peak plasma concentration (4.73 ± 0.05 µg/mL) at 45 min. Cefquinome was not detected in plasma samples collected after 18 h post intramuscular administration in either treatment group.

Following intramuscular administration of cefquinome alone, the absorption rate constant (K_α), absorption half-life ($t_{1/2K\alpha}$), volume of distribution (Vd_{area}), total body clearance (Cl_B) and elimination half-life ($t_{1/2\beta}$) of cefquinome were 1.27 ± 0.17 h^{-1}, 0.61 ± 0.10 h, 2.07 ± 0.36 L/kg, 0.12 ± 0.01 L/h/kg and 12.29 ± 2.62 h, respectively, while AUC, AUMC and MRT were 16.65 ± 0.57 µg.h/mL, 157.05 ± 37.93 µg.h^2/mL and 9.14 ± 1.83 h. The various pharmacokinetic parameters of cefquinome (2 mg/kg) following a single dose intramuscular administration alone and in tolfenamic acid (2 mg/kg) treated sheep are presented in Table 2.

Table 2. Pharmacokinetic parameters of cefquinome (2 mg/kg) following a single dose, intramuscular administration alone and in co-administration with tolfenamic acid (2 mg/kg) treated sheep (Mean ± SE, n = 6)

Pharmacokinetic parameter	Units	Mean ± SE	
		Normal/Healthy	Tolfenamic acid-treated
K_{α}	h^{-1}	1.27 ± 0.17	2.75 ± 0.17**
$t_{½K\alpha}$	h	0.61 ± 0.10	0.26 ± 0.01**
$t_{½\beta}$	h	12.29 ± 2.62	9.00 ± 0.51
C_{max}	µg/mL	4.36 ± 0.10	4.73 ± 0.05*
T_{max}	h	0.75 ± 0.01	0.75 ± 0.01
$AUC_{(0-\infty)}$	µg.h/mL	16.65 ± 0.57	17.52 ± 0.14
AUMC	$\mu g.h^2/mL$	157.05 ± 37.93	127.55 ± 5.24
$Vd_{(area)}$	L/kg	2.07 ± 0.36	1.48 ± 0.08
$Cl_{(B)}$	L/h/kg	0.12 ± 0.01	0.11 ± 0.01
MRT	h	9.14 ± 1.83	7.27 ± 0.27

*Significant at P<0.05, **Significant at P<0.01 when compared with respective values of cefquinome alone (IM) and in tolfenamic acid (IM) treated sheep. K_a: Absorption rate constant, $t_{1/2ka}$: Absorption half-life, $t_{1/2\beta}$: Elimination half-life, C_{max}: Maximum drug concentration, T_{max}: Time of maximum observed concentration in serum, $AUC_{0-\infty}$: Area under the curve, AUMC: Area under first moment of curve, Vd_{area}: Apparent volume of distribution, $Cl_{(B)}$: Total body clearance, MRT: Mean residence time.

Discussion

In the present study, following intramuscular administration of cefquinome in tolfenamic acid-treated sheep, a significant decrease in absorption half-life ($t_{½Ka}$) (0.26 ± 0.01 h) and maximum drug concentration (4.73 ± 0.05 µg/mL) was observed, whereas all other pharmacokinetic parameters were not significantly altered as compared to healthy sheep.

A significant increase in peak plasma concentration (C_{max}) of cefquinome was observed in tolfenamic acid co-administrated sheep (4.73 ± 0.05 µg/mL) as compared to cefquinome alone treated sheep (4.36 ± 0.10 µg/mL). Similarly, several other authors have also reported an increase in the C_{max} of different cephalosporins following its co-administration with anti-inflammatory drugs. The present finding was in accordance with the report of an increase in C_{max} of cefepime following concurrent intramuscular ketoprofen administration (PATEL et al., 2012a). Likewise, a significant increase in the C_{max} of ceftizoxime following concomitant intramuscular administration of paracetamol was observed in cross-bred calves by SINGH et al. (2008). The finding of the present study is in agreement with the significant increase in C_{max} of cefazolin following intramuscular co-administration of phenylbutazone, as reported in rabbits by CARBON et al. (1981).

Also BAROT (2011) reported a significant increase in the C_{max} of cefpirome, following co-administration of ketoprofen in goats. In the same way, the enhanced C_{max} of cefotiam and ceftriaxone, following concomitant administration of diclofenac in rabbits, was observed by JOLY et al. (1988). In contrast to the present study, no significant difference in the C_{max} of cefepime was observed following concomitant intramuscular administration of ketoprofen in goats (PATEL et al., 2012b).

In the present study, following intramuscular administration of cefquinome with tolfenamic acid in sheep, the major pharmacokinetics parameters were not significantly altered in comparison to sheep administered cefquinome alone. Similarly, the major pharmacokinetic parameters of cefmenoxime remained unaffected following concomitant diclofenac sodium administration in rabbits (JOLY et al., 1988) which supports the results of our study. No significant alterations were found in the major pharmacokinetic parameters of cefepime following its concomitant intramuscular administration with ketoprofen in sheep (PATEL et al., 2012a), which is in agreement with the present study. Likewise, the pharmacokinetic parameters of cefepime remained unaltered following concomitant administration with ketoprofen in goats (PATEL et al., 2012b), which is in accordance with our study. Similarly, BAROT (2011) also reported no noteworthy alteration in the major pharmacokinetics parameters of cefpirome following co-administration of ketoprofen in goats. Furthermore, PATIL et al. (2012) also reported no significant alteration in the pharmacokinetics of cefepime following co-administration of ketoprofen in cow calves which also supports our study.

In contrast to the present study, RANJAN et al. (2009) reported significant alterations in distribution half-life ($t_{1/2\alpha}$), AUC, total body clearance (Cl_B) and $Vd_{(area)}$ of ceftizoxime following co-administration of meloxicam in sheep. A significant increase in the value of elimination half-life ($t_{1/2\beta}$) of cefazolin was also reported following co-administration with phenylbutazone in rabbits by CARBON et al. (1981). Asignificant increase in the AUC and $t_{1/2\beta}$ of ceftizoxime was reported following concomitant administration with paracetamol in crossbred calves by SINGH et al. (2008). However, a significant increase in the absorption half-life ($t_{½K\alpha}$) of cefepime was reported following co-administration with ketoprofen in sheep by PATEL et al. (2012a). Reports of alterations in the pharmacokinetic parameters of cephalosporin when co-administered with NSAIDs may be due to differences in the species of animal and the chemical nature of the drugs.

The findings of the present study showed that no significant alterations in the major pharmacokinetic parameters of cefquinome were observed following its concomitant administration with tolfenamic acid in sheep. So, it may be concluded that intramuscular administration of tolfenamic acid (2 mg/kg) may be successfully co-administrated with cefquinome (2 mg/kg) for combating bacterial infections with an inflammatory condition in sheep.

References

AL-TAHER, A. Y. (2010): Pharmacokinetics of cefquinome in camels. J. Anim. Vet. Adv. 9, 848-852.

BAROT, D. (2011): Studies on pharmacokinetics of cefpirome in rats and effect of fever and co-administration of ketoprofen on pharmacokinetics of cefpirome along with its safety in goats. Ph.D. Thesis. Anand Agricultural University. Gujarat, India.

CARBON, C., A. CONTREPOIS, Y. NIVOCHE, M. GRANDJEAN, S. DECOURT, N. P. CHAU (1981): Effects of phenylbutazone on extravascular diffusion, protein binding and urinary excretion of cefazolin in rabbits. J. Pharmacol. Exper. Therap. 218, 537-543.

DINAKARAN, V., V. DUMKA, B. RANJAN, R. BALAJE, P. K. SIDHU (2013): Pharmacokinetics following intravenous administration and pharmacodynamics of cefquinome in buffalo calves. Trop. Anim. Health Prod. 45, 1509-1512.

DUMKA, V. K., V. DINAKARAN, B. RANJAN, S. RAMPAL (2013): Comparative pharmacokinetics of cefquinome following intravenous and intramuscular administration in goats. Small Ruminant Res. 113, 273-277.

GUERIN-FAUBLEE, V., G. CARRET, P. HOUFFSCHMITT (2003): *In vitro* activity of 10 antimicrobial agents against bacteria isolated from cows with clinical mastitis. Vet. Rec. 152, 466-471.

HWANG, Y. H., I. B. SONG, H. K. LEE, T. W. KIM, M. S. KIM, J. H. LIM, B. K. PARK, H. I. YUN (2011): Pharmacokinetics and bioavailability of cefquinome in rabbits following intravenous and intramuscular administration. J. Vet. Pharmacol. Ther. 34, 618-620.

JOLY, V., B. PANGON, N. BRION, J. M. VALLOIS, C. CARBON (1988): Enhancement of the therapeutic effect of cephalosporins in experimental endocarditis by altering their pharmacokinetics with diclofenac. J. Pharmacol. Exper. Therap. 246, 695-700.

KANKAANRANTA, H., E. MOILANEN, H. VAPAATALO (1991): Tolfenamic acid inhibits iankotriene B4-induced chemotaxis of polymorphonuclear leukocytes *in vitro*. Inflam. 15, 137-143.

LIMBERT, M., D. ISERT, D. KLESEL, A. MARKUS, K. SEEGER, G. SEIBERT, E. SCHRINNER (1991): Antibacterial activity *in-vitro* and *in-vivo* and pharmacokinetics of cefquinome (HR 111V), a new broad spectrum cephalosporin. Antimicrob. Agents Chemother. 35, 14-19.

LINDEN, I., J. PARANTAINEN, H. VAPAATALO (1976): Inhibition of prostaglandin biosynthesis by tolfenamic acid *in vitro*. Scand. J. Rheumatol. 5, 129-132.

PATEL, H., N. PATEL, S. PATEL, S. DEWDA, J. PATEL, S. BHAVSAR, A. THAKER (2012b): Effect of ketoprofen co-administration and febrile State on Pharmacokinetic of cefepime in goats. Asian J. Anim. Vet. Adv. 7, 46-53.

PATEL, N., H. PATEL, S. PATEL, S. DEWDA, J. PATEL, S. BHAVSAR, A. THAKER (2012a): Effect of ketoprofen co-administration or febrile state on pharmacokinetic of cefepime in sheep. Vet. Arhiv 82, 473-481.

PATIL, A., S. BHAVSAR, H. PATEL, N. PATEL, S. PATEL, S. DEWDA, J. PATEL, A. THAKER (2012): Effect of ketoprofen co-administration on pharmacokinetic of cefepime in cow calves. Inter J. Vet. Sci. 1, 72-75.

PROUDMAN, K. E., R. M. McMILLAN (1991): Are Tolfenamic acid and tenidap dual inhibitors of 5-lipoxygenase and cyclo-oxygenase? Agents Actions 34, 121-124.

RANJAN, A., B. ROY, R. PRASAD, R. RANJAN (2009): Effect of meloxicam co-treatment on pharmacokinetics of ceftizoxime in sheep. J. Vet. Pharmacol. Toxicol. 8, 22-25.

REJHOLEC, V., H. VAPAATALO, O. TOKOLA, G. GOTHONI (1979): A comparative, double-blind study on Tolfenamic acid in the treatment of rheumatoid arthritis. Scand. J. Rheumatol. 24, (Suppl.) S13-S16.

SADER, H. S., R. N. JONES (1993): The fourth-generation cephalosporins: antimicrobial activity and spectrum definitions using cefpirome as an example. Antimicrob. Newsl. 9, 9-16.

SHPIGEL, N. Y., P. SCHMID (1997): Contribution to the treatment of acute bovine mastitis with cefquinome. Tierärztl. Praxis 25, 200-206.

SIDHU, P. K., M. F. LANDONI, P. LEES (2006): Pharmacokinetic and pharmacodynamic interactions of tolfenamic acid and marbofloxacin in goats. Res. Vet. Sci. 80, 79-90.

SINGH, R., R. K. CHAUDHARY, V. K. DUMKA (2008): Influence of paracetamol on the pharmacokinetics and dosage regimen of ceftizoxime in cross bred calves. Israel J. Vet. Med. 63, 72-76.

SONG, I. B., T. W. KIM, H. G. LEE, M. S. KIM, Y. H. HWANG, B. K. PARK, J. H. LIM, H. I. YUN (2013): Influence of the injection site on the pharmacokinetics of cefquinome following intramuscular injection in piglets. J. Vet. Med. Sci. 75, 89-92.

THOMAS, E., G. MARTIN, B. VOSS, A. BOETTNER, P. POMMIER, W. LOEHLEIN, K. HELLMANN (2002): A comparative field study of the efficacy of cefquinome and amoxycillin against acute meningitis of weaned piglets. Pig Journal 50, 28-41.

TOHAMY, M. A. (2011): Age-related intramuscular pharmacokinetics of cefquinome in sheep. Small Ruminant Res. 99, 72-76.

UNEY, K., F. ALTAN, M. ELMAS (2011): Development and validation of a high-performance liquid chromatography method for determination of cefquinome concentrations in sheep plasma and its application to pharmacokinetic studies. Antimicrob. Agents Chemother. 55, 854-859.

WINTHER, L., K. E. BAPTISTE, C. FRIIS (2011): Antimicrobial disposition in pulmonary epithelial lining fluid of horses, Part III. cefquinome. J. Vet. Pharmacol. Ther. 34, 482-486.

XIE, W., X. ZHANG, T. WANG, S. DU (2013): Pharmacokinetic analysis of cefquinome in healthy chickens. Br. Poult. Sci. 54, 81-86.

YANG, D. W., Z. L. CHEN, H. Z. DING, X. G. SHEN, S. S. XU, X. Y. GU (2009): Pharmacokinetics and bioavailability of cefquinome in pigs. Chin. J. Vet. Sci. 29, 1182-1185.

YUAN, L., J. SUN, R. WANG, L. SUN, L. ZHU, X. LUO, B. FANG, Y. LIU (2011): Pharmacokinetics and bioavailability of cefquinome in healthy ducks. Am. J. Vet. Res. 72, 122-126.

Received: 5 April 2014
Accepted: 25 November 2014

RANA, M. P., K. A. SADARIYA, A. M. THAKER: Učinak tolfenaminske kiseline na farmakokinetiku cefkvinoma nakon njihove istodobne intramuskularne primjene u ovaca. Vet. arhiv 85, 283-292, 2015.

SAŽETAK

Istražena je farmakokinetika cefkvinoma (2 mg/kg) nakon njegove intramuskularne primjene i istodobno u kombinaciji s tolfenaminskom kiselinom (2 mg/kg) u ovaca. Koncentracija cefkvinoma u plazmi bila je određena visokotlačnom tekućinskom kromatografijom. Vršna koncentracija cefkvinoma u plazmi (C_{max}) 0,75 h nakon primjene jedne njegove doze iznosila je 4,36 ± 0,10 µg/mL. Poluživot apsorpcije cefkvinoma ($t_{1/2K\alpha}$) iznosio je 0,61 ± 0,10 h, njegov volumen raspodjele (Vd_{area}) 2,07 ± 0,36 L/kg, ukupni klirens iz organizma (Cl_B) 0,12 ± 0,01 L/h/kg te poluživot izlučivanja ($t_{1/2\beta}$) 12,29 ± 2,62 h. Nakon istodobne intramuskularne primjene tolfenaminske kiseline nisu ustanovljene značajne promjene u većini farmakokinetičkih pokazatelja cefkvinoma osim za C_{max} i konstante stope apsorpcije (K_α) koji su bili značajno povećani dok je $t_{1/2}$ K_a bio značajno smanjen u usporedbi s primjenom samog cefkvinoma. Farmakokinetički pokazatelji cefkvinoma (2 mg/kg) proizašli iz ovog istraživanja upućuju na zaključak da se cefkvinom može u ovaca primijeniti istodobno s tolfenaminskom kiselinom za liječenje bakterijskih infekcija s upalnim promjenama.

Ključne riječi: farmakokinetika, cefkvinom, tolfenaminska kiselina, ovce